A PROSPECTIVE STUDY OF PRESCRIBING PATTERN OF ANTIHYPERTENSIVE DRUGS IN A TERTIARY CARE HOSPITAL

A Dissertation submitted to

The Tamil Nadu Dr. M.G.R. Medical University,
Chennai - 600 032

In partial fulfillment of the award of the degree of
MASTER OF PHARMACY
IN
BRANCH - PHARMACY PRACTICE

Submitted by
NAME: FATHIMA BEVI. A
REG.No. 261540203

Under the Guidance of
Dr. N. VENKATESWARAMURTHY, M Pharm., Ph.D.,
DEPARTMENT OF PHARMACY PRACTICE

J.K.K. NATTRAJA COLLEGE OF PHARMACY
KUMARAPALAYAM – 638 183
TAMILNADU

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"A Prospective Study of Prescribing Pattern of Antihypertensive Drugs in A Tertiary Care Hospital"** submitted by the student bearing **[REG.No.261540203]** to **"The Tamil Nadu Dr. M.G.R. Medical University"**, Chennai, in partial fulfillment for the award of Degree of **Master of Pharmacy** in **Pharmacy Practice** was evaluated by us during the examination held on.....

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Dr. R. Sambath Kumar, M.Pharm, Ph.D.,
Principal & Professor

Dr. N. Venkateswaramurthy, M.Pharm, Ph.D.,
Head of the Department & Guide

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Place: Kumarapalayam
Date:

Dr. R. SAMBATH KUMAR, M.Pharm, Ph.D.,
Professor & Principal,
J.K.K.Nattraja College of Pharmacy.
Kumarapalayam-638 183.

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Place: Kumarapalayam
Date:

Dr. N. VENKATESHWARAMURTHY, M.Pharm, Ph.D.,
Professor and Head,
Department of Pharmacy Practice,
J.K.K.Nattraja College of Pharmacy.
Kumarapalayam-638 183.

DECLARATION

I do here by declared that the dissertation **"A Prospective Study of Prescribing Pattern of Antihypertensive Drugs in A Tertiary Care Hospital",** submitted to "**The Tamil Nadu Dr. M.G.R Medical University"**, Chennai, for the partial fulfillment of the degree of **Master of Pharmacy** in **Pharmacy Practice,** It is a bonafide research work has been carried out by me during the academic year 2016-2017, under the guidance and supervision of **Dr. N. Venkateswaramurthy, M.Pharm.,Ph.D.,** Professor, Head, Department of Pharmacy practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam

Date:

Mrs. FATHIMA BEVI A

[REG.No.261540203]

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Mrs. FATHIMA BEVI A

[REG.No.261540203]

J.K.K.NATTRAJA ETHICS COMMITTEE

J.K.K.NATTRAJA COLLEGE OF PHARMACY

P.B.No 151, Natarajapuram, NH-47 (Salem to Coimbatore),
Komarapalayam - 638 183. Namakkal District, Tamil Nadu

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To
Mr. N. Venkateswaramurthy, M.Pharm, PhD.,
Department of Pharmacy Practice,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam – 638183,
India.

Dear Venkateswaramurthy,

The proposal entitled **"A prospective study of prescribing pattern of antihypertensive drugs in a tertiary care hospital"** was reviewed by the ethics committee in its meeting held on 28.*06.2016* and permission is granted to you to carry out the study.

Thanking you,

Yours faithfully,

Dr. A. Sivakumar
Chairman of Ethics Committee

ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin-Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitor
ACEI	Angiotensin-Converting Enzyme Inhibitors
ACOG	American College Of Obstetricians And Gynecologists
ACT	Artemisinin Combination Therapy
ACTH	Adrenocorticotropic Hormone
AHA	American Heart Association
ALT	Alanine Amino Transferase
AME	Apparent Mineralo Corticoid Excess
ARB	Angiotensin Receptor Blocker
AST	Aspartate Amino Transferase
AT_1	Angiotensin 1
AT_2	Angiotensin 2
ATP	Adenosine Triphosphate
BBS	Beta Blockers
BMI	Body Mass Index
BP	Blood Pressure
BP	Blood Pressure
CAD	Coronary Artery Disease

CAM	Complementary And Alternative Medicine
CCB	Calcium Channel Blockers
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CKD ND	Non–Dialysis-Dependent CKD
CNS	Central Nervous System
CRP	C-Reactive Protein
CT	Computed Tomography
CVD	Cardio Vascular Disease
DBP	Diastolic Blood Pressure
DBP	Diastolic Blood Pressure
FHR	Foetal Heart Rate
GFR	Glomerular Filtration Rate
GRA	Glucocorticoid Remediable Aldosteronism
HBP	High Blood Pressure
HDL	High-Density Lipoprotein
HDP	Hypertensive Disorders Of Pregnancy
HELLP	Hemolysis, Elevated Levels Of Liver Enzymes, And Low Platelet Count
HLA	Human Leukocyte Antigen
HR	Heart Rate
ICU	Intensive Care Unit
IFN	Interferon
IHD	Ischemic Heart Disease

IL-6	Interleukin-6
IUGR	Intrauterine Growth Restriction
JNC	Joint National Committee
JNC	Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure
LBW	Low Birth Weight
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LV	Left Ventricular
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
NHBPEP	National High Blood Pressure Education Program
NK	Natural Killer
NKF	National Kidney Foundation
NO	Nitric Oxide
NSAID	Nonsteroidal Anti-Inflamatory Agents
NSAID	Nonsteroidal Anti-Inflammatory Drug
PCR	Protein/Creatinine Ratio
PE	Pre-Eclampsia
PEACE	Prevention Of Events With Angiotensin-Converting Enzyme Inhibitor Therapy
PI	Pulsatility Index
PIH	Pregnancy Induced Hypertension

PTH	Para Thyroid Hormone
RAAS	Renin-Angiotensin-Aldosterone System
RI	Resistance Index
ROS	Reactive Oxygen Species
S/D	Systolic/Diastolic Ratio
SBP	Systolic Blood Pressure
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
SGA	Small For Gestational Age
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TC	Total Cholesterol
TGF	Transforming Growth Factor
TSH	Thyroid Stimulating Hormone
UKPDS	United Kingdom Of Prospective Diabetes Study
VLDL	Very Low-Density Lipoprotein
WHO	World Health Organization

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INTRODUCTION

1.1 HYPERTENSION

Hypertension is a strong independent risk factor for coronary and cerebrovascular diseases, as well as for heart failure, atrial fibrillation and chronic renal failure[1], thus substantially contributing to the global burden of disease.

Hypertension is a common disease that is defined simply as persistently elevated arterial blood pressure (BP). Increasing awareness and diagnosis of hypertension and improving control of BP with appropriate treatment are considered critical Public health initiatives to reduce cardiovascular morbidity and mortality.

Moreover, it is well known that reducing blood pressure (BP) in hypertensive patients is associated with a significant reduction in the rate of cardiovascular complications and decline in renal function[2,3].

The 7th report of Joint National Committee on prevention, detection, evaluation, and treatment of hypertension, defined hypertension as systolic blood pressure (SBP) of 140mmHg or more (or) diastolic blood pressure (DBP) of 90mmHg or more[4].

1.1.1 Classification of Hypertension:

It is a heterogeneous medical condition. In most patients it results from unknown pathophysiologic etiology (essential or primary hypertension). While this form of hypertension cannot be cured, it can be controlled. A small percentage of patients have a specific cause of their hypertension (secondary hypertension). It is defined simply as persistently elevated arterial BP.

Table. 1 Classification of Blood Pressure

Classification	Systolic BP(mmHg)	Diastolic BP(mmHg)
Normal	Less than 120	Less than 80
Prehypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	≥ 160	≥100

1.1.2 ETIOLOGICAL CLASSIFICATION

In most patients it results from unknown pathophysiologic etiology (essential or primary hypertension). While this form of hypertension cannot be cured, it can be controlled. A small percentage of patients have a specific cause of their hypertension (secondary hypertension). There are many potential secondary causes that are either concurrent medical conditions or endogenously induced. If the cause of secondary hypertension can be identified, hypertension in these patients potentially can be cured.

1.1.2.1 Primary hypertension

Essential (also known as primary) hypertension is high blood pressure for which a specific cause is unknown. The majority (90-95%) of hypertension cases falls into this category.

Factors implicated in primary hypertension include:

- Age
- Genetics
- Environment
- Weight
- Race.

Over 90% of individuals with hypertension have essential hypertension (primary hypertension)[5]. Numerous mechanisms have been identified that may contribute to the pathogenesis of this form of hypertension, so identifying the exact underlying abnormality is not possible. Hypertension often runs in families, indicating that genetic factors may play an important role in the development of essential hypertension. Data suggest that there are monogenic and polygenic forms of BP dysregulation that may be responsible for essential hypertension. Many of these genetic traits feature genes that affect sodium balance, but genetic mutations altering urinary kallikrein excretion, nitric oxide release, aldosterone excretion, other adrenal steroids, and angiotensinogen are also documented.

1.1.2.2 Secondary hypertension

Secondary hypertension is high blood pressure that is a symptom of an identified medical problem, such as kidney disease. If the medical problem is fixed, the high blood pressures will decrease[6].

Causes of secondary hypertension include:

• Renal disease

• Pregnancy

• Hormonal factors

• Drug-induced factors (e.g. oral contraceptives, corticosteroids).

About 10% of patients have secondary hypertension, where either a comorbid disease or a drug is responsible for elevating BP [5]. In most of these cases, renal dysfunction resulting from chronic kidney disease or renovascular disease is the most common secondary cause[8]. Certain drugs, either directly or indirectly, can cause hypertension or exacerbate hypertension by increasing BP.. Some of these agents are herbal products. Although these are not technically drugs, they have been identified as causes of elevated BP and secondary hypertension. When a secondary cause is identified, removing the offending agent or treating/correcting the underlying comorbid condition should be the first step in management.

Table: 2 Secondary Causes of Hypertension

Disease	Drugs associated with hypertension in humans
Chronic kidney disease Cushing's syndrome Coarctation of the aorta Obstructive sleep apnea Parathyroid disease Pheochromocytoma Primary aldosteronism Renovascular disease Thyroid disease	**Prescription drugs** Corticosteroids, ACTH Estrogens (usually oral contraceptives with high estrogenic activity) Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors Phenylpropanolamine and analogues Cyclosporine and tacrolimus Erythropoetin Sibutramine Antidepressants (especially venlafaxine), bromocriptine, buspirone, carbamazepine, clozapine, desfulrane, ketamine, metoclopramide Clonidine/ β-blocker combination Pheochromocytoma: β-blocker without α-blocker first **Other Natural Products** Cocaine and cocaine withdrawal Ma huang, "herbal ecstasy", other phenylpropanolamine analogues Nicotine and withdrawal, anabolic steroids, narcotic

	withdrawal, methylphenidate, phencyclidine, ketamine, ergotamine and other ergot-containing herbal products, St. John's wort **Food Substances** Sodium Ethanol Licorice Tyramine-containing foods if taking a monoamine oxidase inhibitor **Chemical Elements and Other Industrial Chemicals** Lead, mercury, thallium and other heavy metals, lithium

1.1.3 EPIDEMIOLOGY

Recent data from the World Health Organization (WHO) indicate that nearly one billion people in the world are suffering from hypertension. Forecasts suggest that, with the aging of the population, this number could reach 1.5 billion by 2025[1].

Reviews of studies on hypertension epidemiology in India have shown high prevalence in both urban and rural areas[7-8].

Worldwide, high blood pressure (HBP) is estimated to cause 7.1 million deaths, about 13 percent of the global fatality total. Across world health organization (WHO) regions, research indicates that about 62 percent of strokes and 49 percent of heart attacks are caused by HBP[9].

Increasing awareness and diagnosis of hypertension and improving control of BP with appropriate treatment are considered critical Public health initiatives to reduce cardiovascular morbidity and mortality.

The "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" provides a new guideline for hypertension prevention and management. According to JNC – 7 guidelines in persons older than 50 years, systolic blood pressure greater than 140 mmHg is a much more important cardiovascular disease (CVD) risk factor than diastolic blood pressure[5].

The WHO estimates that 600 million people with HBP are at risk of heart attack, stroke and cardiac failure. Worldwide, Indo-Asian people are among the populations at highest risk for cardiovascular disease[10].

Evidence also suggests that associations between body mass index (BMI), percentage of body fat and chronic disease may increase the risk of cardiovascular diseases. Because of the observed differences between populations, the International Association for the Study of Obesity and the International Obesity Task Force have suggested lower BMI cutoff values for the definitions of overweight (23.0–24.9 kg/m^2) and obesity (25.0 kg/m^2 or greater) in Asian populations[11].

Dubey VD [12] carried out one of the earliest study in India (1954), documented 4% prevalence of hypertension (criteria:>160/95) amongst. During 1984-87 Gopinath and Chadha *et al.,* [10] reported the prevalence of hypertension (criteria: $\geq$160/90) to be 11% among males and 12% among females in the urban areas and 4% and 3% respectively in rural areas. Another two studies carried out in rural areas[11] (1994-95) demonstrated 4.5% prevalence of hypertension (JNC V criteria) while urban areas had a higher prevalence of 45% during 1996-97[18].

1.1.4 SIGNS AND SYMPTOMS

- Bluish lips and skin (cyanosis)
- Blurred vision
- Chest pain or pressure
- Confusion
- Dizziness
- Fainting spells (syncope)
- Fatigue / decreased energy
- Headache
- Palpitations (a strong feeling of a fast heartbeat)
- Papilledema (swelling of the optic disc)
- Racing pulse
- Edema (swelling in the ankles or legs)
- Shortness of breath, at rest and /or during periods of exercise[19].

1.1.4.1 Risk Factors for Hypertension

Known modifiable risk factors for hypertension are:

- Obesity
- Excessive intakes of salt, fat (especially saturated fat), and calories
- Inadequate physical activity
- Uncontrolled hyperglycaemic states
- High alcohol consumption

- Tobacco use
- Low potassium intake
- Sleep apnoea
- Psychosocial stress is often implicated but difficult to measure

1.1.5 DIAGNOSIS

Essential hypertension is usually asymptomatic. The primary physical finding is elevated BP. The diagnosis of hypertension cannot be made based on one elevated BP measurement. The average of two or more measurements taken during two or more clinical encounters should be used to diagnose hypertension [5]. Thereafter, this BP average can be used to establish a diagnosis and then to classify the stage of hypertension present in the patient.

1.1.5.1 Measuring blood pressure

Sphygmomanometer

Indirect measurement of BP using a sphygmomanometer is a common routine medical screening tool that should be conducted at every health care encounter[6]. The appropriate procedure to measure BP has been described by the American Heart Association (AHA)[13]. It is imperative that the measurement equipment (inflation cuff, stethoscope, manometer) meet certain national standards. These standards use criteria to ensure maximum quality and precision with measurement.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) provides information about BP during daily activities and sleep[14].These devices use either a microphone to measure Korotkoff sounds or a cuff that senses arterial waves using oscillometric

techniques. Twenty-four hour BP monitoring provides multiple readings during all of a patient's activities.

Ambulatory BP values are usually lower than clinic readings. Awake hypertensive individuals have an average BP of >135/85 mmHg, and during sleep, >120/75 mmHg. ABPM also provides a measure of the percentage of BP readings that are elevated, the overall BP load, and the extent of BP fall during sleep. In addition, it was reported recently that ABPM patients whose 24-hour BP exceeded 135/85 mmHg were nearly twice as likely to have a cardiovascular disease[15].

Laboratory and Other Diagnostic Tests

The routine laboratory tests recommended before initiation of therapy include: electrocardiogram; urinalysis; blood glucose and hematocrit; serum potassium; creatinine (or corresponding estimated glomerular filtration rate) and calcium[16], lipid profile (9-12 hours fasting) which includes high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides. Optional tests include measurement of urinary albumin excretion or albumin/creatinine ratio. More extensive investigation for identifiable causes is not generally indicated unless BP control is not achieved.

Table. 3 SCREENING tests for identifiable hypertension

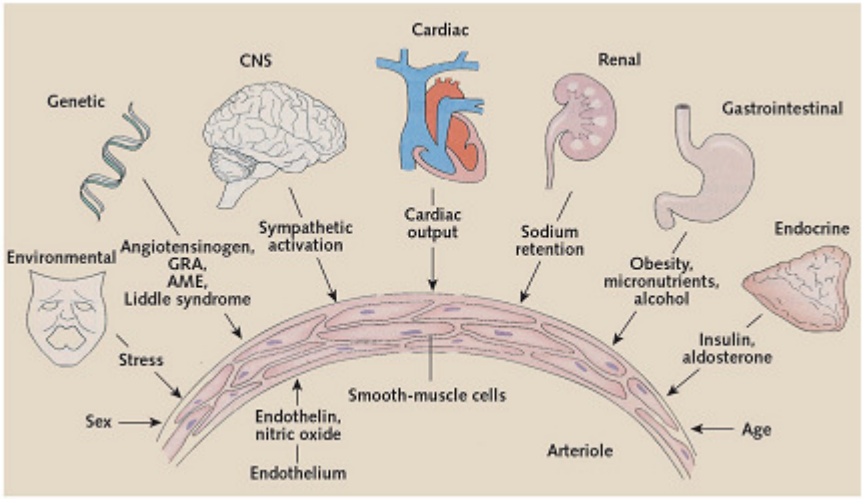
DIAGNOSIS	DIAGNOSTIC TEST
Chronic kidney disease	Estimated Glomerular Filtration Rate
Coarctation of the aorta	CT angiography
Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy	History; dexamethasone suppression test
Drug induced/related	History; drug screening
Pheochromocytoma	24-hour urinary metanephrine and normetanephrine
Primary aldosteronism and other mineralocorticoid specific measurements of other mineralocorticoids	24-hour urinary aldosterone level or excess states
Renovascular hypertension	Doppler flow study; magnetic resonance angiography
Sleep apnea	Sleep study with O2 saturation
Thyroid/parathyroid disease	Thyroid stimulating hormone(TSH); serum Parathyroid hormone(PTH)

1.1.6 PATHOPHYSIOLOGY [6,17]

A clear understanding of arterial BP and regulation is needed to manage hypertension appropriately and to understand antihypertensive drug therapy mechanistically. Multiple factors that control BP are potential contributing components in the development of hypertension. These include malfunctions in either humoral (i.e., the renin-angiotensin-aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal neuronal mechanisms, defects in peripheral autoregulation, and disturbances in sodium, calcium, and natriuretic hormone. Many of these factors are cumulatively affected by the multifaceted RAAS, which ultimately regulates arterial BP.

1.1.6.1 Potential mechanisms of pathogenesis

Blood pressure is the mathematical product of cardiac output and peripheral resistance. Increased blood pressure can result from increased cardiac output and/or increased total peripheral resistance.



AME-apparent mineralocorticoid excess; **CNS**-central nervous system; **GRA**-glucocorticoid-remediable aldosteronism.

Increased cardiac output	**Increased peripheral resistance**
Increased cardiac preload: ▪ Increased fluid volume from excess sodium intake or renal sodium retention (from reduced number of nephrons or decreased glomerular filtration) Venous constriction: ▪ Excess stimulation of the RAAS ▪ Sympathetic nervous system overactivity	Functional vascular constriction: ▪ Excess stimulation of the RAAS ▪ Sympathetic nervous system overactivity ▪ Genetic alterations of cell membranes ▪ Endothelial-derived factors Structural vascular hypertrophy: ▪ Excess stimulation of the RAAS ▪ Sympathetic nervous system overactivity ▪ Genetic alterations of cell membranes ▪ Endothelial-derived factors ▪ Hyperinsulinemia resulting from obesity or the metabolic syndrome

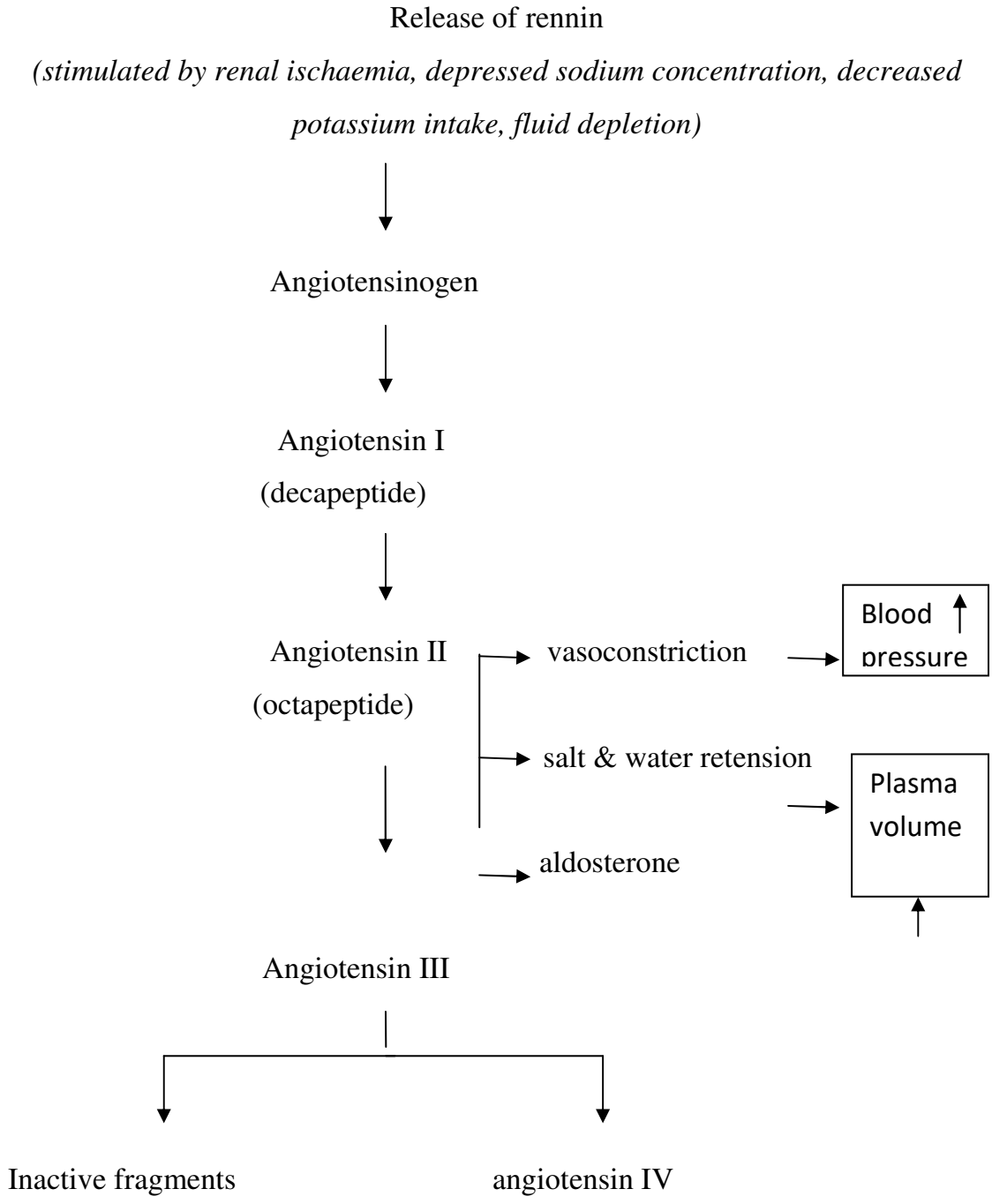
1.1.6.2 Humoral mechanisms

Several humoral abnormalities may be involved in the development of essential hypertension. These abnormalities may involve the the renin-angiotensin-aldosterone system, natriuretic hormone and hyperinsulinemia.

The renin-angiotensin-aldosterone system (RAAS)

The RAAS is a complex endogenous system that is involved with most regulatory components of arterial BP. Activation and regulation are governed primarily by the kidney. The RAAS regulates sodium, potassium, and fluid balance. Therefore, this system significantly influences vascular tone and sympathetic nervous system activity and is the most influential contributor to the homeostatic regulation of BP. Renin is an enzyme that is stored in the juxtaglomerular cells, which are located in the afferent arterioles of the kidney. The release of renin is modulated by several factors: intrarenal factors (e.g., renal perfusion pressure, catecholamines, and angiotensin II) and extrarenal factors (e.g., sodium, chloride, and potassium).

Renin catalyzes the conversion of angiotensinogen to angiotensin I in the blood. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE). After binding to specific receptors (classified as either AT_1 or AT_2 subtypes), angiotensin II exerts biologic effects in several tissues. The AT1 receptor is located in brain, kidney, myocardium, peripheral vasculature, and the adrenal glands. These receptors mediate most responses that are critical to cardiovascular and kidney function. The AT_2 receptor is located in adrenal medullary tissue, uterus, and brain. Stimulation of the AT_2 receptor does not influence BP regulation. Circulating angiotensin II can elevate BP through pressor and volume effects. The pressor effects include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and centrally mediated increases in sympathetic nervous system activity. Angiotensin II also stimulates aldosterone synthesis from the adrenal cortex. This leads to sodium and water reabsorption that increases plasma volume, total peripheral resistance, and ultimately, BP.


Release of rennin
(stimulated by renal ischaemia, depressed sodium concentration, decreased potassium intake, fluid depletion)
Angiotensinogen
Angiotensin I
(decapeptide)
Angiotensin II
(octapeptide)
vasoconstriction
Blood pressure
salt & water retension
Plasma volume
aldosterone
Angiotensin III
Inactive fragments
angiotensin IV

Natriuretic hormone

Natriuretic hormone inhibits sodium and potassium ATPase and thus interferes with sodium transport across cell membranes. Inherited defects in the kidney's ability to eliminate sodium can cause an increased blood volume. A compensatory increase in the concentration of circulating natriuretic hormone theoretically could increase urinary excretion of sodium and water. However, this same hormone is also thought to block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular concentration of sodium ultimately would increase vascular tone and BP.

Insulin resistance and hyperinsulinemia

Increased insulin concentrations may lead to hypertension because of increased renal sodium retention and enhanced sympathetic nervous system activity. Moreover, insulin has growth hormone–like actions that can induce hypertrophy of vascular smooth muscle cells. Insulin also may elevate BP by increasing intracellular calcium, which leads to increased vascular resistance. The exact mechanism by which insulin resistance and hyperinsulinemia occur in hypertension is unknown. However, this association is strong because many of the criteria used to define this population (elevated blood pressure, obesity, dyslipidemia, and elevated blood glucose) are often present in hypertensive patients[6].

Neuronal regulation

The central and autonomic nervous systems are intricately involved in the regulation of arterial BP. A number of receptors that either enhance or inhibit norepinephrine release are located on the presynaptic surface of sympathetic terminals. The α and β presynaptic receptors play a role in negative and positive feedback to the norepinephrine containing vesicles located near the neuronal ending. Stimulation of presynaptic α-receptors ($\alpha 2$) exerts a negative inhibition on norepinephrine release. Stimulation of presynaptic β-receptors facilitates further release of norepinephrine. Sympathetic neuronal fibers located on the surface of

effector cells innervate the α- and β-receptors. Stimulation of postsynaptic α-receptors (α1) on arterioles and venules results in vasoconstriction. There are two types of postsynaptic β-receptors, β1 and β2. Both are present in all tissue innervated by the sympathetic nervous system. However, in some tissues, β1-receptors predominate, and in other tissues, β2-receptors predominate. Stimulation of β1-receptors in the heart results in an increase in heart rate and contractility, whereas stimulation of β2-receptors in the arterioles and venules causes vasodilation.

Peripheral autoregulatory components

Abnormalities in renal or tissue autoregulatory systems could cause hypertension. It is possible that a renal defect in sodium excretion may develop first, which can then cause resetting of tissue autoregulatory processes, resulting in a higher arterial BP. The kidney usually maintains normal BP through a volume-pressure–adaptive mechanism. When BP drops, the kidneys respond by increasing retention of sodium and water. These changes lead to plasma volume expansion, which increases BP. Conversely, when BP rises above normal, renal sodium and water excretion are increased to reduce plasma volume and cardiac output. This ultimately will maintain homeostatic BP conditions.

Vascular endothelial mechanisms

Vascular endothelium and smooth muscle play important roles in regulating blood vessel tone and BP. These regulating functions are mediated through vasoactive substances that are synthesized by endothelial cells. It has been postulated that a deficiency in the local synthesis of vasodialating substances (e.g., prostacyclin and bradykinin) or excess vasoconstricting substances (e.g., angiotensin II and endothelin I) contribute to essential hypertension, atherosclerosis, and other diseases. Nitric oxide is produced in the endothelium, relaxes the vascular epithelium, and is a very potent vasodilator. The nitric oxide system is an important regulator of arterial BP. Hypertensive patients may have an intrinsic deficiency in nitric oxide release, resulting in inadequate vasodilatation. Although the exact role of nitric oxide in hypertension is unclear, it may be a pharmacologic target in the future.

Electrolytes and other chemicals

Epidemiologic and clinical data have associated excess sodium intake with hypertension. Population-based studies indicate that high-salt diets are associated with a high prevalence of stroke and hypertension. Conversely, low-salt diets are associated with a low prevalence of hypertension. Clinical studies have shown consistently that dietary sodium restriction lowers BP in many (but not all) patients with elevated BP.

Altered calcium homeostasis also may play an important role in the pathogenesis of hypertension. A lack of dietary calcium hypothetically can disturb the balance between intracellular and extracellular calcium, resulting in an increased intracellular calcium concentration. This imbalance can alter vascular smooth muscle function by increasing peripheral vascular resistance.

In the case of potassium, Potassium depletion may increase peripheral vascular resistance, but the clinical significance of small serum potassium concentration changes is unclear. Furthermore, data demonstrating reduced cardiovascular risk with dietary potassium supplementation are very limited.

1.1.7 TREATMENT

1.1.7.1 GOALS of therapy

The ultimate goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. most persons with hypertension, especially those >50 years of age, the primary focus should be on attaining the systolic blood pressure (SBP) goal. Treating systolic blood pressure (SBP) and diastolic blood pressure (DBP) to target <140/90 mmHg is associated with a decrease in cardiovascular disease (CVD) complications. In patients with hypertension and diabetes or renal disease, the BP goal is <130/80 mmHg[4].

1.1.7.2 General approach to treatment

Patients should be placed on both lifestyle modifications and drug therapy concurrently. Lifestyle modifications alone are not considered adequate for patients with hypertension or hypertensive patients with diabetes and chronic kidney disease.

The choice of initial drug therapy depends on the degree of BP elevation and the presence of compelling indications. Most patients with stage 1 hypertension should be treated initially with a thiazide-type diuretic. For most patients with more severe BP elevation (stage 2 hypertension), combination drug therapy, with one of the agents preferably being a thiazide type-diuretic, is recommended.

1.1.7.3 Non pharmacological therapy

Life style modification:

All patients with prehypertension and hypertension should be prescribed lifestyle modifications. These approaches are recommended by the JNC7 [5] and provide small to moderate reductions in SBP. Aside from lowering BP in patients with known hypertension, lifestyle modification can decrease the progression to hypertension in patients with prehypertension BP values[18]. In a number of hypertensive patients with relatively good BP control while on single antihypertensive drug therapy, sodium reduction and weight loss may allow withdrawal of drug therapy [19,20].

A sensible dietary program is one that is designed to reduce weight gradually for overweight and obese patients and one that restricts sodium intake with only moderate alcohol consumption. Successful implementation of dietary lifestyle modifications by clinicians requires aggressive promotion through reasonable patient education, encouragement, and continued reinforcement. Patients may better understand the rationale for dietary intervention in hypertension if they are provided the following observations and facts:

1. Hypertension is two to three times more prevalent in overweight as compared with lean persons.
2. Over 60% of hypertensive persons are overweight.
3. Weight loss, even as little as 10 pounds, can decrease BP significantly in hypertensive overweight individuals [21].
4. Abdominal obesity is associated with the metabolic syndrome, which is a precursor to hypertension and insulin-resistance syndrome that may progress to type 2 diabetes, dyslipidemia, and ultimately, cardiovascular disease[22].
5. Diets rich in fruits and vegetables and low in saturated fat have been shown to lower BP in hypertensive individuals [23,24].
6. Although some hypertensive patients are not salt-sensitive, most people experience some degree of SBP reduction with sodium restriction[6,25].

A controlled diet plan is needed that is rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat. The recommended restriction is less than 2.4 g (100 mEq) sodium per day. Patients should be aware of the multiple sources of dietary sodium (e.g., processed meats, soups, and table salt) so that they may follow this restriction. Excessive alcohol use can either cause or worsen hypertension. Hence, Alcohol intake should be limited. Carefully designed programs of physical activity can lower BP. Regular aerobic exercise for at least 30 minutes a day most days of the week is ideal for most patients.

1.1.7.4 Pharmacological Therapy:

There are 9 classes of anti hypertensive drugs. Diuretics, β-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers are considered primary antihypertensive agents.

These agents, either alone or in combination, should be used to treat the majority of hypertensive patients.

More than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensive agents selected from different drug classes.

Several of these classes (i.e., diuretics, β-blockers, and calcium channel blockers) have subclasses with significant differences in mechanism of action, clinical use., α-Blockers, central α2-agonists, adrenergic inhibitors, and vasodilators are considered alternative drug classes..

According to JNC7 guidelines thiazide-type diuretics is preferred whenever possible as first-line therapy for most patients [5]. This recommendation is specifically for those without compelling indications. However, diuretics are also useful agents in hypertensive patients with compelling indications, but they are not always the first agent recommended.

Table.4 Primary antihypertensive agents

Class	Subclass	Drug	Usual Dose Range, mg/day
Diuretics	Thiazides	Chlorthalidone	6.25–25
		Hydrochlorothiazide	12.5–50
		Indapamide	1.25–2.5
		Metolazone	0.5
	Loop diuretics	Loops Bumetanide	0.5–4
		Furosemide	20–80
		Torsemide	5
	Potassium sparing	Amiloride	5–10
		Amiloride/ Hydrochlorothiazide	5–10/50–100
		Triamterene	50–100
		Triamterene/ Hydrochlorothiazide	37.5–75/25–50
	Aldosterone Antagonists	Eplerenone	50–100
		Spironolactone	25–50
		Spironolactone/ Hydrochlorothiazide	25–50/25–50
Angiotensin converting enzyme inhibitors		Benazepril	10–40
		Captopril	12.5–150
		Enalapril	5–40
		Fosinopril	10–40
		Lisinopri	10–40
		Moexipril	7.5–30
		Perindopril	4–16
		Quinapril	10–80

	Ramipril	2.5–10
	Trandolapril	1–4
Angiotensin II receptor Blockers	Candesartan	8–32
	Eprosartan	600–800
	Irbesartan	150–300
	Losartan	50–100
	Olmesartan	20–40
	Telmisartan	20–80
	Valsartan	80–320

β-Blockers	Cardioselective	Atenolol	25–100
		Betaxolol	5–20
		Bisoprolol	2.5–10
		Metoprolol	50–200
		Nebivolol	2.5-5
	Nonselective	Nadolol	40–120
		Propranolol	80–320
		Timolol	10–40
	Intrinsic sympathomimetic activity	Acebutolol	200–800
		Carteolol	2.5–10
		Penbutolol	10–40
		Pindolol	10–60
	Mixed α- and β-blockers	Carvedilol	12.5–50
		Labetolol	200–800
Calcium channel Blockers	Dihydropyridines	Amlodipine	2.5–10
		Felodipine	5–20
		Isradipine	5–10
		Nicardipine	60–120
		Nifedipine	30–90
		Nisoldipine	10–40
	Non-Dihydropyridines	Diltiazem	180–360
		Verapamil	180–480

Table.5 Alternative antihypertensive agents

Class	Drug	Usual Dose Range, mg/day
α1-Blockers	Doxazosin	1–8
	Prazosin	2–20
	Terazosin	1–20
Central α2-agonists	Clonidine	0.1–0.8
	Methyldopa	250–1000
Peripheral adrenergic antagonist	Reserpine	0.05–0.25
Direct arterial vasodilators	Minoxidil	10–40
	Hydralazine	20–100

1.1.7.4.1 Individual Antihypertensive Agents [4,21,26]

Diuretics

Diuretics, preferably a thiazide, are first-line agents for most patients with hypertension. Moreover, when combination therapy is needed in hypertension to control BP, a diuretic is recommended as one of the agents used [5]. Four subclasses of diuretics are used in the treatment of hypertension: thiazides, loop diuretics, potassium-sparing agents, and aldosterone antagonists Thiazide diuretics have additional actions that may further explain their antihypertensive effects. Thiazides mobilize sodium and water from arteriolar walls. This effect would lessen the amount of physical encroachment on the lumen of the vessel created by excessive accumulation of intracellular fluid. As the diameter of the lumen relaxes and increases, there is less resistance to the flow of blood, and peripheral vascular resistance drops further. Thiazides also are postulated to cause direct relaxation of vascular smooth muscle.

Angiotensin-converting enzyme inhibitors (ACEI)

ACE inhibitors are considered second-line therapy to diuretics in most patients with hypertension [5]. ACE inhibitors have many roles for patients with hypertension and coexisting conditions. ACE facilitates the production of angiotensin II, which has a major role in the regulation of arterial BP. ACE, is distributed in many tissues and is present in several different cell types, but its principal location is in endothelial cells. Therefore, the major site for angiotensin II production is in the blood vessels, not the kidney. ACE inhibitors block the conversion of angiotensin I to angiotensin II. This latter substance is a potent vasoconstrictor that also stimulates aldosterone secretion. ACE inhibitors also block the degradation of bradykinin and stimulate the synthesis of other vasodilating substances, including prostaglandin and prostacyclin. The observation that ACE inhibitors lower BP in patients with normal plasma rennin activity suggests that bradykinin and perhaps tissue production of ACE are important in hypertension. Increased bradykinin enhances the BP-lowering effects of ACE inhibitors.

Angiotensin II receptor blockers

Angiotensin II is generated by two enzymatic pathways: the RAAS, which involves ACE, and an alternative pathway that uses other enzymes such as chymases. ACE inhibitors inhibit only the effects of angiotensin II produced through the RAAS, whereas ARBs inhibit angiotensin II from all pathways. It is unclear how these differences affect tissue concentrations of ACE. Because of these differences, ACE inhibitors only partially block the effects of angiotensin II. ARBs directly block the angiotensin II type 1 (AT_1) receptor that mediates the known effects of angiotensin II in humans: vasoconstriction, aldosterone release, sympathetic activation, antidiuretic hormone release, and constriction of the efferent arterioles of the glomerulus. They do not block the angiotensin II type 2 (AT_2) receptor. Therefore, beneficial effects of AT_2 receptor stimulation (i.e., vasodilation, tissue repair, and inhibition of cell growth) remain intact when ARBs are used. Unlike ACE inhibitors, ARBs do not block the breakdown of bradykinin. Therefore, some of the beneficial effects of bradykinin such as vasodilation (which can enhance BP lowering), regression of myocyte hypertrophy and fibrosis, and increased levels of tissue plasminogen activator are not present with ARB therapy.

Calcium channel blockers (CCB)

CCBs are not first-line agents but are very effective antihypertensive agents, especially in African-American patients. They have compelling indications in high coronary disease risk and in diabetes. However, with these compelling indications, they are in addition to or in replacement of other antihypertensive drug classes. Some data indicated that dihydropyridines may not provide as much protection against cardiac events when compared with "conventional" therapy (diuretics and β-blockers) or ACE inhibitors in uncomplicated hypertension [27]. Contraction of cardiac and smooth muscle cells requires an increase in free intracellular calcium concentrations from the extracellular fluid. When cardiac or vascular smooth muscle is stimulated, voltage-sensitive channels in the cell membrane are opened, allowing calcium to enter the cells. The influx of extracellular calcium into the cell releases stored calcium from

the sarcoplasmic reticulum. As intracellular free calcium concentration increases, it binds to a protein, calmodulin, which then activates myosin kinase, enabling myosin to interact with actin to induce contraction. CCBs work by inhibiting influx of calcium across the cell membrane. There are two types of voltage-gated calcium channels: a high-voltage channel (L-type) and a low-voltage channel (T-type). Currently available CCBs only block the L-type channel, which leads to coronary and peripheral vasodilation.

β-blockers

β-Blockers have been used in several large outcome trials in hypertension. Several mechanisms of action have been proposed for β-adrenoreceptor blockers (β-blockers), but none of them alone has been shown to be associated consistently with a reduction in arterial BP. β-Blockers have negative chronotropic and inotropic cardiac effects that reduce cardiac output, which explains some of the antihypertensive effect. However, cardiac output falls equally in patients treated with β-blockers regardless of BP lowering. *β*-Blockers that possess a greater affinity for β1-receptors than β2-receptors are *cardioselective.* Both *β*1- and *β*2-adrenoceptors are distributed throughout the body, but they concentrate differently in certain organs and tissues. There is a preponderance of β1- receptors in the heart and kidney and a preponderance of *β*2-receptors in the lungs, liver, pancreas, and arteriolar smooth muscle. *β*1-Receptor stimulation increases heart rate, contractility, and renin release. β2-Receptor stimulation results in bronchodilation and vasodilation. Cardioselective β-blockers are less likely to provoke bronchospasm and vasoconstriction.

α1-Blockers

They work in the peripheral vasculature and inhibit the uptake of catecholamines in smooth muscle cells, resulting in vasodilation and BP lowering.

Central α2-agonists

These agents lower BP primarily by stimulating α2-adrenergic receptors in the brain. This stimulation reduces sympathetic outflow from the vasomotor center in the brain and increases vagal tone. It is also believed that peripheral stimulation of presynaptic α2-receptors may further reduce sympathetic tone. Reduced sympathetic activity, together with enhanced parasympathetic activity, can decrease heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes.

1.1.7.4.2 COMBINATION THERAPY:

Choice / selection of combination therapy [JNC VII guidelines]

According to algorithm for the treatment of hypertension in JNC VII additional drugs can add until goal blood pressure is achieved.

According to JNC VII majority of diabetic patients will require two or more drugs to achieve BP control.

According to JNC VII guideline a diuretic is recommended for majority of hypertensive patients especially in decrease glomerular filtration rate or in heart failure.

Table: 5 choice of drug combination

	ARB	*Diuretics*	*β-Blockers*	*ACEI*	*CCB*	*Central sympatholytics*
ARB		✓		✓	✓	
Diuretics	✓		✓	✓		✓
β-Blockers		✓				
ACEI	✓	✓			✓	
CCB	✓			✓		
Central sympatholytic		✓				

CCB: Calcium Channel Blockers **ARB:** Angiotensin II Receptor Blockers

ACEI: Angiotensin converting enzyme inhibitors

Table -6: Mechanism of action of combined drug class:

Combinations	Mechanisms	
ARB-Diuretic	ARBs cause the antagonism of angiotensin II at the vascular and myocardial level by direct AT-1 receptor blockade	Thiazide diuretic blocks sodium chloride reabsorption at the distal convoluted tubule
β-Adrenoreceptor Antagonist-Diuretic	The β-adrenoreceptor blocker inhibits activation by direct suppression of renin release, inhibit β-adrenergic sympathetic stimulation decreasing myocardial contractility and heart rate	Diuretics as above
ACEI-Diuretic	ACEI cause the removal of the angiotensin II effect (vasoconstriction, stimulation of aldosterone secretion) and enhancement of kinin-mediated vasodilation	Diuretics as above
		The calcium antagonists

ACEI-CCB	ACEI as above	de-crease vascular resistance by vascular smooth muscle relaxation
ARB-CCB	ARBs as above	CCBs as Above
ACE-ARB Inhibitors	ACEI as above	ARBs as above
Centrally Acting Agents-Diuretic	Clonidine acts by decreasing sympathetic outflow by stimulating pre synaptic α2-adrenoceptors in the vasomotor centre of the CNS.	Diuretics as above

Disease processes affected by anti-hypertensive drugs:

- ***Diabetes*** – Beta-blockers and thiazide diuretics may make glycemic control difficult. ACE inhibitors can protect the kidney.
- ***Coronary Artery Disease*** – Beta-blockers offer a mortality benefit (in general). Short-acting calcium channel blockers can worsen ischemia.
- ***Congestive Heart Failure*** (compensated vs. un-compensated) – Beta-blockers offer a mortality benefit as do ACE inhibitors. Beta-blockers should not be used in uncompensated CHF.
- ***Hyperlipidemia*** – Beta-blockers and thiazide diuretics may affect lipid profile unfavorably.
- ***COPD/Asthma*** – Beta-blockers need to be used with caution.
- ***Peripheral Vascular Disease*** – Beta-blockers need to be used with discretion.
- ***Renal Artery Stenosis*** (bilateral vs. unilateral) – ACE inhibitor or ARB's are relatively contraindicated.

- ***Cardiac Conduction Defects*** – Beta-blockers, diltiazem and verapamil can exacerbate conduction defects.
- ***Benign Prostatic Hypertrophy*** – Alpha-1 blockers can provide symptomatic improvement.
- ***Depression*** – Beta-blockers may exacerbate.
- ***Raynaud's Syndrome*** – Beta-blockers may exacerbate.
- ***Renal Failure*** – ACE inhibitors may cause a reduction in renal performance
- ***Pregnancy*** – ACE inhibitors and ARB's are contraindicated.
- ***Aortic Stenosis*** – Vasodilators need to be introduced with caution.
- ***Hyperuricemia (Gout)*** – Thiazide diuretics may increase uric acid levels.

REVIEW OF LITERATURE

Tiwari[28] ***et al., (2004)*** conducted a study about drug prescribing trend of antihypertensive agents at Panjab University Health Centre in India. The study was conducted in order to establish the drug-prescribing trend of anti-hypertensive agents. The information was collected from prescription of outpatient department. World Health Organisation-based prescription-auditing proforma was used for data collection. This study revealed that most of the male patients were on monotherapy. In the monotherapy category, four classes of drugs were used. These were calcium channel blockers, beta-blockers, ACE inhibitors and diuretics. Among monotherapy drugs, calcium channel blockers were prescribed most whereas diuretics were least used. Overall, 57.8 percent patients were treated with a single anti-hypertensive drug and 42.2 percent were treated with anti-hypertensive drug combinations. The study highlights certain shortcomings in the existing prescribing practice. There is a considerable scope for improvement, particularly the under-utilization of diuretics in the present prescribing pattern of antihypertensive drugs.

Akici[29] ***et al., (2007)*** conducted a study on Antihypertensive drug utilization at health centers in a district of Istanbul. Objective of the study was to evaluate antihypertensive drug utilization in hypertension, because irrational use of antihypertensives has considerable clinical and economical consequences. A total of 297 hypertensive patients who accepted to participate in the study were evaluated by a face-to-face questionnaire and a copy of their prescriptions were collected for prescription analysis. They concluded that that *General Practitioners (GPs)* working at primary healthcare centers were rational in terms of antihypertensive drug choice. However, they poorly applied rational pharmacotherapy principles such as (a) writing a "good'' prescription which is easily readable by the pharmacist and the patient and that contains full essential information; (b) a medical examination of the patient to assess her/his current clinical condition; and (c) taking care of not prescribing drugs with potential interaction like antihypertensives and NSAIDs together.

Adeel Aslam[30] ***et al.,*** **(2007)** conducted a comparative study on antihypertensive therapy using single drug versus multiple drugs in pregnancy induced hypertension. The objective of the study was to assess the stress response in severe pregnancy induced hypertensive patients on different drug regimen during preoperative and postoperative period. 40 patients of severe pregnancy induced hypertensives were induced in this study. 20 patients were placed on a single standard antihypertensive i.e. alpha methyldopa and 20 were put on a combination of alpha methyldopa with long acting nifedipine or amlodipine. Both these groups underwent caesarean section. The stress response in both these groups was carefully analyzed and compared with a special note on any untoward effect on the mother or fetus. The results from this trial clearly demonstrated that patients on combined drug therapy showed better stress response during perioperative and postoperative period. Thus the authors concluded that in severe PIH patients undergoing caesarean section good feto-maternal outcome was obtained on combination antihypertensive drug therapy as compared to patients receiving single anti-hypertensive drug.

White[31] ***et al., (2010)*** conducted a study to investigate the management of hypertension in patients with diabetes mellitus, living in a rural setting southeastern Australia. Patients with either diagnosed hypertension or high blood pressure who attended the clinic were included in their study. The awareness and control of hypertension was compared between patients with and without diabetes mellitus. A total of 449 patients with hypertension were analyzed. One hundred twenty-one (26.9%) had hypertension and diabetes mellitus, and 328 (73.1%) had hypertension without diabetes mellitus. Hypertension awareness (61.2% versus 36.9%, P=0.014) and control (17.4% versus 7.0%, P=0.040) were significantly better in the hypertensive patients with diabetes mellitus than in the hypertensive patients without diabetes mellitus. Antihypertensive medication use was also significantly higher in patients with diabetes mellitus than in patients without diabetes mellitus (one antihypertensive medication, 41.3% versus 25.0%, P=0.045).The authors concluded that Awareness and control of hypertension were suboptimal in the patients in the present study. Diabetes mellitus, however, was associated with both higher awareness

and better control of hypertension than having hypertension alone. This may be partially due to a higher use of antihypertensive medications by patients with diabetes mellitus.

Balakeshwa[32] *et al.,* (2008) studied the prescribing pattern of antihypertensive therapy in Medical Wards at a Teaching Hospital. It was conducted in the General medicine unit of JSS Medical College Hospital, Mysore. This study was intended to systematically assess the prescribing pattern of antihypertensive in patients with mild to moderate essential hypertension. It was a prospective and observational study conducted over a period of eight months. Primary hypertensive patients of either sex aged greater than or equal to18 years and fulfill JNC-7 criteria were enrolled. All enrolled patients were followed until their discharge. They concluded as beta-blockers and diuretics were widely used as mono and combination therapy in treating mild to moderate primary hypertension.

Garcia[33] *et al., (2004)* conducted a study on use of Antihypertensive drugs in Spain. The data was obtained from the data base of the Spanish ministry of Health. This study was aimed to describe the pattern of use in Spain from 1995 to 2001, its compliance with guidelines, and its economic impact. Aim of the study was the impact of angiotensin II receptor antagonists on the consumption of the drugs from other therapeutic subgroups. Information on drug utilization was obtained from the ECOM database of the Spanish Ministry of Health, which records the number of packages charged to the National Health System. They concluded that the consumption of antihypertensive drugs in Spain has increased remarkably in last 7 years. Likewise cost also increased proportionately, although the contributions of different therapeutic subgroups have been unequal. The impact of angiotensin II receptor antagonists has been considerable, both on consumption and on costs.

Etuk[34] *et al., (2008)* Conducted prescription pattern of anti-hypertensive drugs in a tertiary health institution in Nigeria. This study examined the pattern of physicians' prescription of antihypertensive drugs and its possible effects on blood pressure control as well as physician's compliance with recommended guidelines.

Records of 145 patients aged 17-91 (mean: 52.6 ± 14.6) years, with male to female ratio of 1:1.2 were randomly selected. Information on antihypertensive prescriptions was recorded. Blood pressure control was defined as systolic and diastolic blood pressure less than 140 mm Hg and 90mmHg, respectively. Information collected from antihypertensive prescription. Their results are consistent with the previously observed benefits of antihypertensive combination therapy, and demonstrate an apparent higher efficacy of calcium channel blocker monotherapy than diuretic monotherapy in blood pressure lowering in the study population. Major limitations of this work include its retrosective nature and the inability to determine the actual patients' adherence to therapy.

Pang-Hsiang[35] *et al.,* (2008) conducted study of Antihypertensive medication prescription patterns and time trends for newly-diagnosed uncomplicated hypertension patients. It was conducted in Taiwan. The aims of this study were to determine the prescription patterns and time trends for antihypertensive medication in newly-diagnosed cases of uncomplicated hypertension in Taiwan and to compare these with current clinical guidelines. A total of 6,536 newly-diagnosed patients with uncomplicated hypertension, aged ≥30 years, were identified from the representative 200,000-person sample in the computerized reimbursement database of the National Health Insurance in Taiwan. According to their study the prescription patterns varied by age, gender and clinical facilities, with mono-therapies being found to be dominant in the first year, albeit declining over time and calcium channel blockers and beta-blockers were the most frequently prescribed antihypertensive drugs, either alone or in combinations. These findings indicate the existence of a gap between current clinical practice and the desired goal of cost-effectiveness in antihypertensive treatment in Taiwan, which should be corrected.

Jeschke[36] *et al.,* (2009) conducted a study on Evaluation of prescribing patterns in a German network of CAM physicians for the treatment of patients with hypertension. The study was aimed to investigate hypertension treatment strategies among physicians specialized in complementary and alternative medicine (CAM) in Germany by analysing prescribing patterns and comparing these to the current

treatment guidelines issued by the German Hypertension Society. In this prospective, multicentre observational study, which included 25 primary care physicians specialized in CAM treatment, prescriptions and diagnoses were analysed for each consecutive hypertensive patient using routine electronic data. Data analysis was performed using univariate statistical tests (Chi square test, Cochran-Armitage trend test). Multiple logistic regression was used to determine factors associated with antihypertensive medication. Most patients were treated with conventional antihypertensive monotherapies. Beta-blockers were the most commonly prescribed monotherapy, followed by ACE inhibitors. Combination treatment usually consisted of two antihypertensive drugs administered either as separate agents or as a coformulation. The most common combination was a diuretic plus an ACE inhibitor. Patient gender, age, and comorbidities significantly influenced which treatment was prescribed. The study concluded as large majority of antihypertensive treatments prescribed by CAM physicians in the present study complied with the current German Hypertension Society treatment guidelines. Deviations from the guidelines were observed in one of every seven patients receiving some form of CAM treatment.

Chantal[37] ***et al., (2001)*** conducted a study on Antihypertensive Drug Therapy in Saskatchewan. The aim of the study was to examine the distribution and determinants of patterns of use of antihypertensive agents in the first 5 years of hypertension treatment in Saskatchewan. Patterns of use and modifications to therapy were derived from a careful examination of medication use in a cohort of 19501 subjects aged 40 to 79 years, without recognized cardiac disease and initiating therapy with an angiotensin -converting enzyme inhibitor, a calcium antagonist, or a b-blocker in Saskatchewan between 1990 and 1993. Angiotensin-converting enzyme inhibitors, followed by calcium antagonists and b-blockers, were the most commonly prescribed agents to initiate treatment in our study population. Patients with diabetes were less likely to be dispensed a b-blocker, as were younger and female patients. Previous visits to a cardiologist decreased the likelihood of receiving combination therapy or angiotensin converting enzyme inhibitors but increased that of using calcium antagonists. Erratic drug-taking behaviors were observed in this Saskatchewan

population. In addition, initial drug use does not seem to be in accordance with the stepped-care approach to hypertension therapy recommended in the Canadian guidelines.

Rajeshwari[38] ***et al., (2007)*** conducted a Drug Utilisation Study in Geriatric Type 2 Diabetic Patients. This study was aimed to evaluate the drug utilisation pattern in geriatric T2DM patients. The study was conducted for a period of 6 months (July 2004 to January 2005) in an out-patient department of a tertiary hospital in Mangalore, Karnataka, India. The medical records of 64 geriatric (age >60 years) type 2 diabetic patients attending the diabetic clinic were reviewed. Drug prescribed mainly for DM and hypertension were included along with other drugs used for their comorbidities. Along with drug regimens, demographic data, age, and gender were recorded. The results were analysed using descriptive statistics. In elderly patients with type 2 diabetes, treatment may be initiated with monotherapy, followed by early intervention with a combination of oral agents, including a sulphonylurea as a foundation insulin secretagogue in addition to a supplemental insulin sensitizer. The study also showed that a combination of sulphonylurea and metformin was most frequently prescribed. Accordingly, metformin is widely regarded as the first drug of choice for most patients with type 2 diabetes mellitus. The study concluded that type 2 diabetic is a progressive and complex disorder that is difficult to treat effectively in the long term. The treatment pattern observed in this study corroborates with the accepted pattern of treatment for DM with hypertension, and/or neuropathy. Metformin, glimepiride, and glibenclamide are most commonly prescribed OADs. Enalapril and ramipril among the ACEIs and atenolol and metaprolol among the beta-blockers are the frequently prescribed antihypertensives.

Supratim[39] ***et al.,*** **(2010)** conducted a cross sectional prescription pattern study in a antihypertensive drug use in patients having comorbid diabetes in a tertiary care hospital manipal. This study aims at analyzing the influence of current guidelines on prescribing in this particular subset of patients. Hypertension and diabetes when present together are associated with a multitude of complications, all of which result in increased morbidity and mortality. This makes it vital to, not only make an early

detection of the disease, but also to make the best use amongst the wide array of drugs available for treatment. Case history of patients having hypertension along with diabetes was noted down from the medical records department. Drugs prescribed in each of these groups were noted and pattern analyzed. A total of 128 prescriptions were of diabetes, amongst which 19 had nephropathy and the remaining 109 did not have nephropathy. The authors concluded that the CCB's were the group of drugs prescribed the most in both diabetes and diabetes associated nephropathy. They were prescribed in 60% patients with diabetes, and 95% of those who had nephropathy. The ACE-inhibitors and ARB's were prescribed in 45% patients with diabetes and 21% in diabetes associated nephropathy. Utilization of ACE- inhibitors is thus well below it is expected to be in both diabetes as well as diabetes associated nephropathy.

Skliros[40] ***et al., (2007)*** Conducted a study to determine hypertension prevalence and levels of awareness, treatment and control of hypertension among diabetic patients using data from the VANK (Valachioti(V), Astras(A), Nemea(N) and Kalavarita(K) study. The sample consisted of 221 men and women (122/99) diagnosed with type 2 diabetes. Semi-structured interviews were conducted with all participants. Controlled hypertension definition was based on having a systolic blood pressure (BP) of <130 mmHg and diastolic BP of <85 mmHg in subjects taking antihypertensive medications. The mean ± SD BP was 141.6 ± 17.4 mmHg and 81.2 ± 9.4 mmHg for systolic and diastolic BPs, respectively. Systolic and diastolic BP was higher in men than in women. The overall prevalence of hypertension was 194/221 (87.7%). In total, 34.1% of patients (66/194) were not aware of having hypertension. Of those who were aware of having hypertension (n = 128, 65.9%), all were treated. Among those treated, only 11 persons (11/194, 5.6%) had systolic BP <130 mmHg and diastolic BP <85 mmHg. Sixty-two (38.7%) had systolic BP <140 mmHg and diastolic BP <90 mmHg. The authors concluded that all of the diagnosed hypertensive patients (n = 128) received antihypertensive drug therapy, in only 8.6% (11/128) the treatment was effective (BP <130/85 mmHg). Translating our findings into clinical practice, there is a need for aggressive treatment of hypertension from primary care

physicians, as well as regular surveillance to detect developing hypertension in diabetic patients.

AIM AND OBJECTIVE

AIM

To study the prescribing pattern of antihypertensive drugs in a tertiary care hospital erode.

OBJECTIVES

- To study the demographic details of the study population.
- To study the BMI and family history of hypertensive patients.
- To determine the occupational status and dietary habits of study population.
- To categorize the prescription pattern and identity the most commonly prescribed antihypertensive drugs

PLAN OF WORK

The entire study was planned to be carried out for a period of 8 months.

The proposal was designed as given below:

- **Proposal**
- **Phase 1**
  - Identify the scope of work
  - Literature survey
  - Study design including designing of questionnaire form
  - Approval from ethical committee.
- **Phase 2**
  - Collection of patient details from patient case reports and by conducting direct patient interview
- **Phase 3**
  - Data analysis
  - Submission of report

METHODOLOGY

The study was aimed to study of prescribing pattern of antihypertive drugs.

Study design:

It is a Prospective observational study.

Study site:

The study was conducted at tertiary care hospital Erode.

Study period:

8 months (From July 2016 to Feb 2017)

Inclusion criteria:

- Patients diagnosed with hypertension.
- Both male and female patients will be included in the study
- Patients above 20 years of age

Exclusion criteria:

- Patients who are not interested to participate in this study
- Patients with doubtful diagnosis
- Patients who are critically ill
- Patients below 20 years of age

Source of data:

The data collects from various sources such as patient case reports and also through direct patient interview

WORK METHODOLOGY

Based on the inclusion and exclusion criteria the study was conducted at tertiary care hospital erode.

- Details regarding demographics, social habits like alcohol intake, drug abuse and smoking, food habit and family history are collected through interviewed patients
- Data about current medical condition and prescription drugs will be collected from patient case report and through direct patient interview.
- The data obtained will be categorized and the current prescribing trends will be evaluated on basis of comparison with the standard treatment guidelines.

Table – 1: Gender wise distribution of hypertensive patients

Gender	*Number of patients (n=360)*	*Percentage(%) of patients*
Male	196	54.44
Female	164	45.55

Figure – 1: Gender wise distribution of hypertensive patients

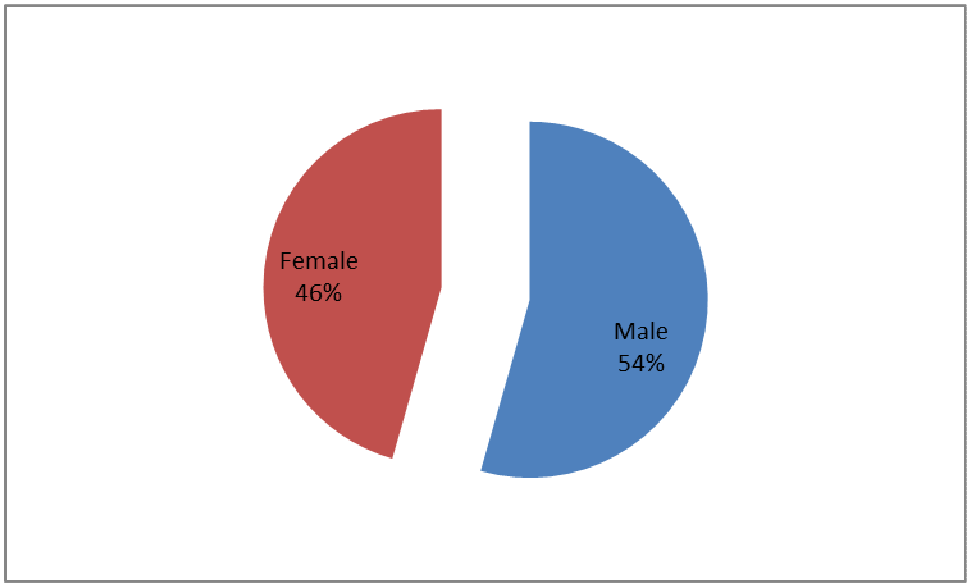


Table – 2: Age wise distribution of hypertensive patients

Age (years)	*Hypertension (n=360)*	*Percentage (%) of patients*
20-24	4	1.11
25-34	18	5
35-44	50	13.88
45-54	82	22.77
55-64	144	40
65+	62	17.22

Figure – 2: Age wise distribution of hypertensive patients

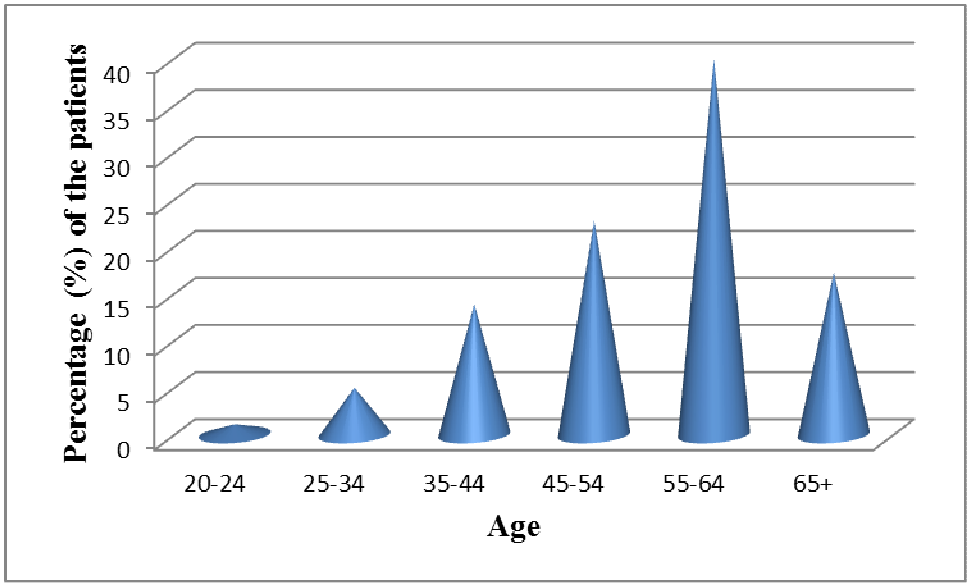
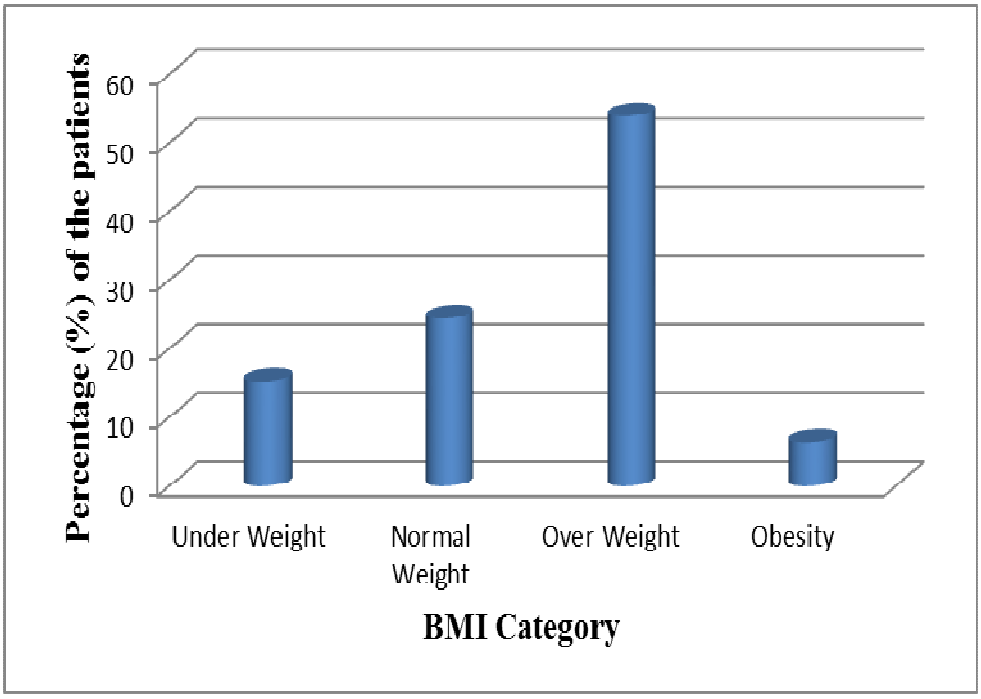


Table – 3: Distribution of hypertension based on body mass index (BMI)

BMI category	*Number of patients (n=360)*	*Percentage (%) of patients*
Under Weight (< 18.5)	55	15.27
Normal Weight (18.5 – 24.9)	88	24.44
Over Weight (25 – 29.9)	194	53.88
Obesity (>30)	23	6.38

Figure – 3: Distribution of Hypertension based on



Body Mass Index (BMI)

Table – 4: Residential area wise distribution of hypertensive patients

Residential area	*Number of patients (n=360)*	*Percentage (%) of patients*
Rural	91	25.27
Urban	186	51.66
Mixed	83	23.05

Figure – 4: Residential area wise distribution of Hypertensive patients

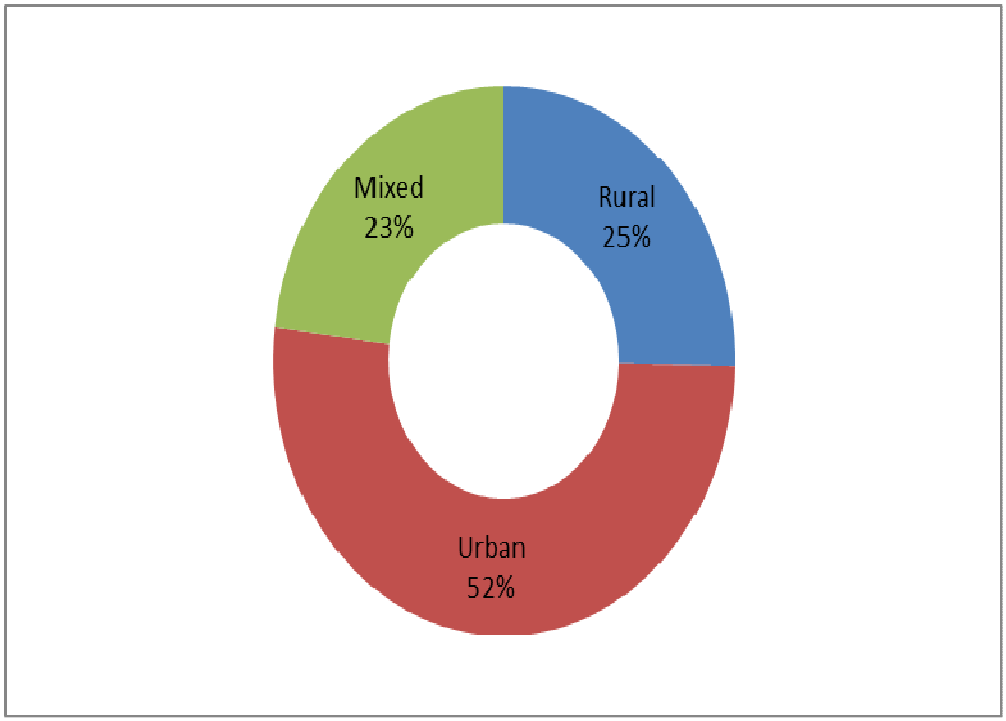
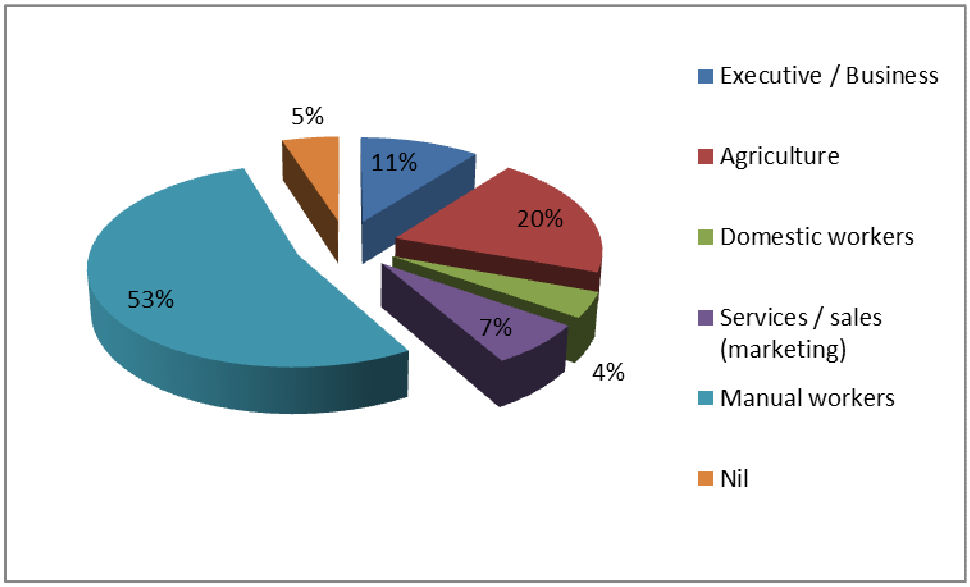


Table – 5: Distribution of hypertension based on occupation

Occupation	*Number of patients (n=360)*	*Percentage (%) of patients*
Executive / Business	38	10.55
Agriculture	72	20
Domestic workers	15	4.16
Services / sales (marketing)	25	6.94
Manual workers	192	53.33
Nil	18	5

Figure – 5: Distribution of Hypertension based on occupation



Occupation

Table – 6: Distribution of hypertension based on sanitation

Sanitation	*Number of patients (n=360)*	*Percentage (%) of patients*
Noise free zone	96	26.66
Noise pollution	264	73.33

Figure – 6: Distribution of hypertension based on sanitation

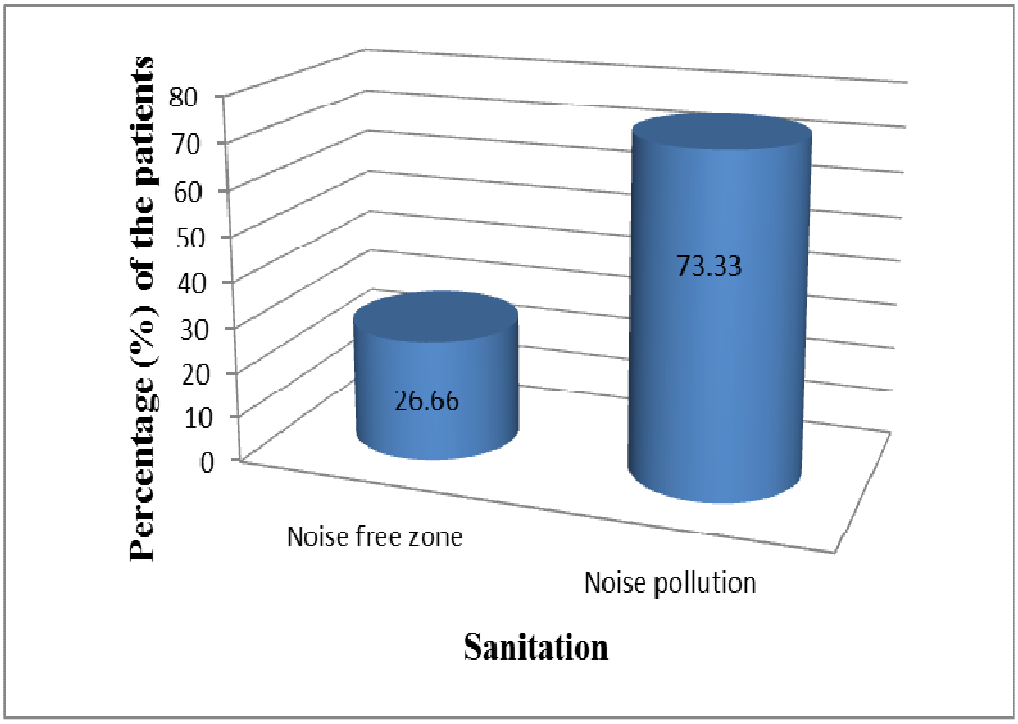


Table – 7: Distribution of hypertension based on sleep disturbance / work stress

Sleep disturbance / stress	*Number of patients (n=360)*	*Percentage (%) of patients*
Normal sleep	95	26.38
Sleep disturbance/Work stress	265	73.61

Figure – 7: Distribution of hypertension based on sleep disturbance / work stress

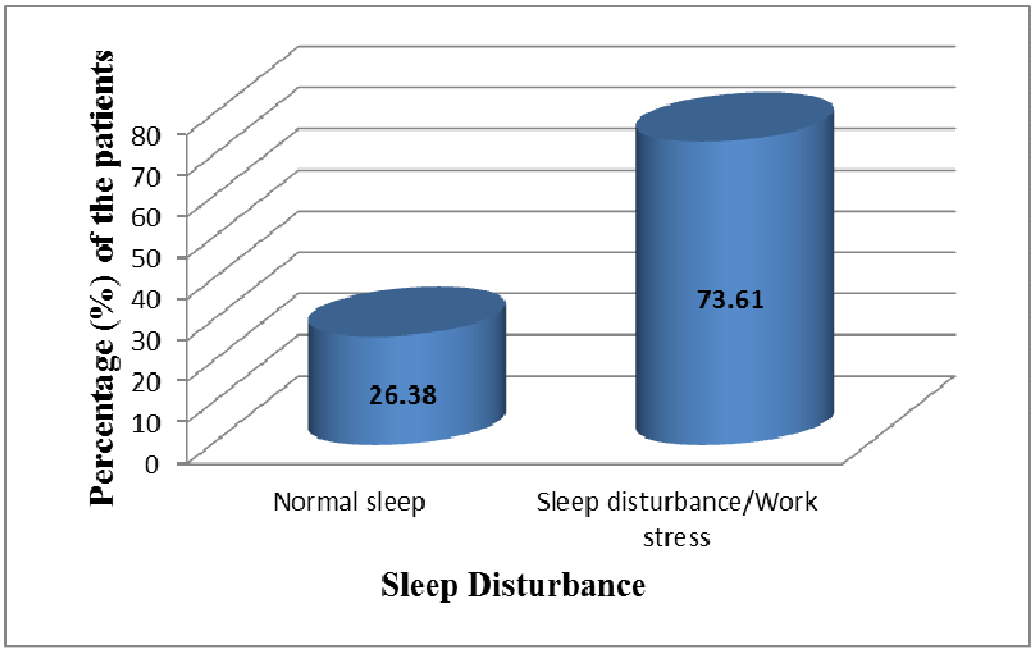


Table – 8: Distribution of hypertension based on food consumption

Food consumption	*Number of patients (n=360)*	*Percentage (%) of patients*
Vegetarian	56	15.55
Vegetarian & Non-vegetarian	304	84.44

Figure – 8: Distribution of Hypertension based on food consumption

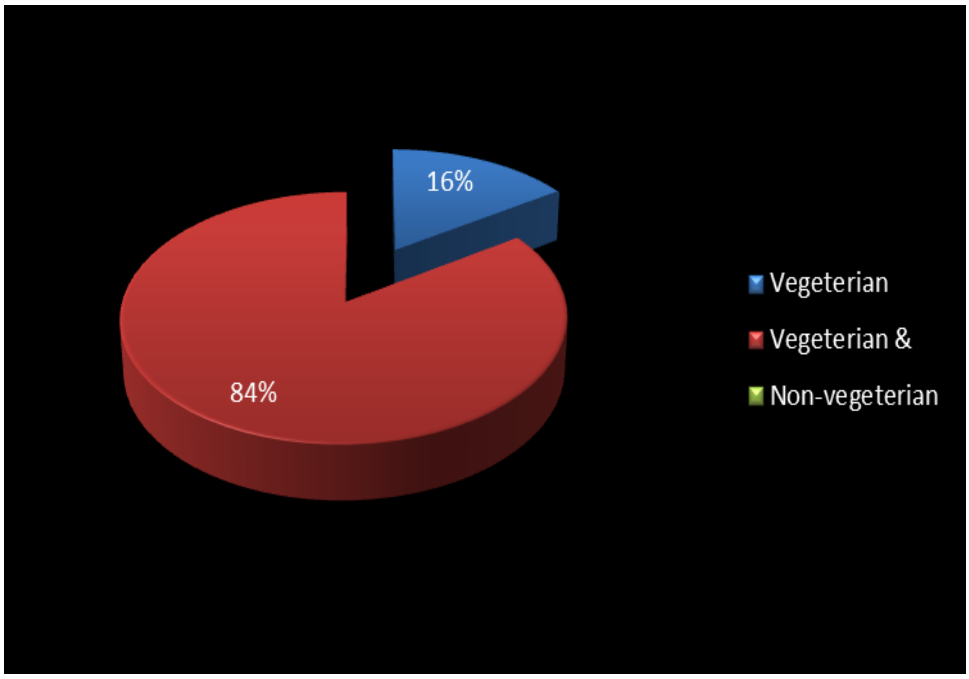


Table – 9: Distribution of hypertension based on oil consumption

Oil consumption	*Number of patients (n=360)*	*Percentage (%) of patients*
Coconut oil	25	6.94
Palm oil	190	52.77
Sunflower oil	94	26.11
Groundnut oil	51	14.16
Soybean oil	0	0

Figure – 9: Distribution of Hypertension based on oil consumption

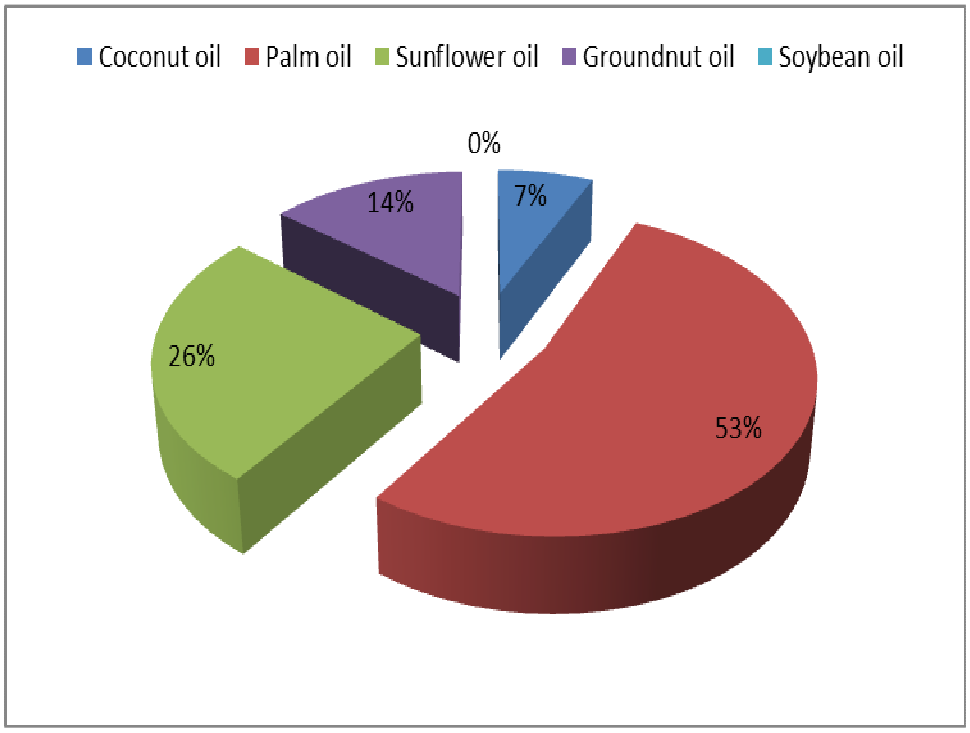


Table – 10: Distribution of hypertension based on consumption of dairy products

Dairy products	*Number of patients (n=360)*	*Percentage (%) of patients*
Milk	30	8.33
Coffee / tea	258	71.66
Health drinks	56	15.55
None	16	4.44

Figure – 10: Distribution of hypertension based on consumption of dairy products

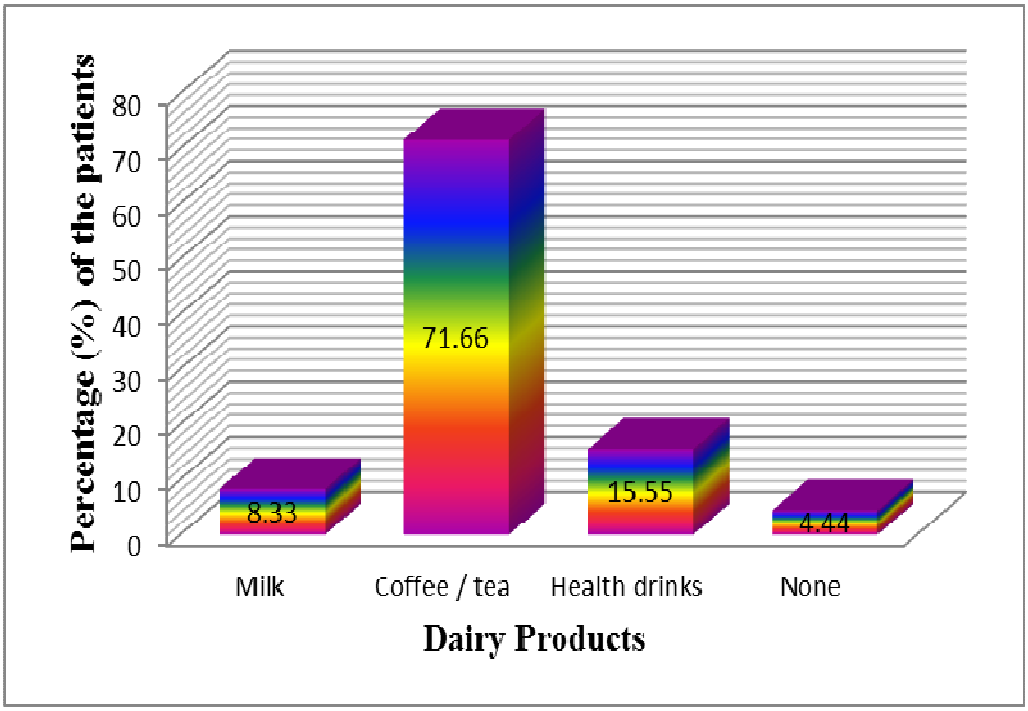


Table – 11: Distribution of hypertension based on behavioral risk factors

Behavioral risk factors	*Number of patients (n=360)*	*Percentage (%) of patients*
Smoking	35	9.72
Tobacco chewing	32	8.88
Alcohol	52	14.44
Smoking+tobacco+alcohol	146	40.55
OTC drugs	20	5.55
None	75	20.83

Figure – 14: Represents distribution of Hypertension based on behavioural risk factors

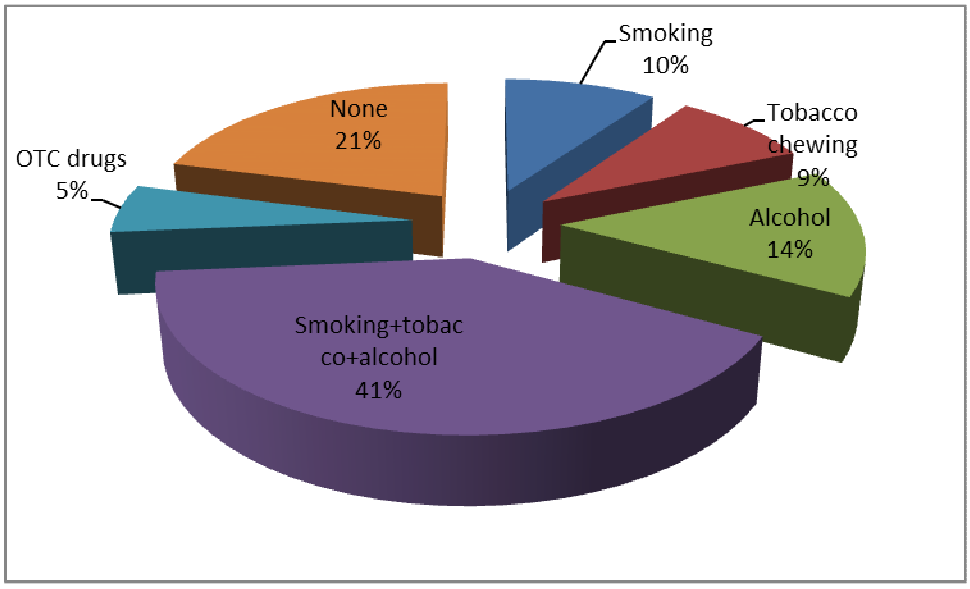


Table – 12: Family history of hypertensive patients

Family relationship	*Number of patients (n=360)*	*Percentage (%) of patients*
Father	153	42.5
Mother	62	17.22
Both	25	6.94
Others	14	3.88
None	106	29.44

Figure – 12: Family history of hypertensive patients

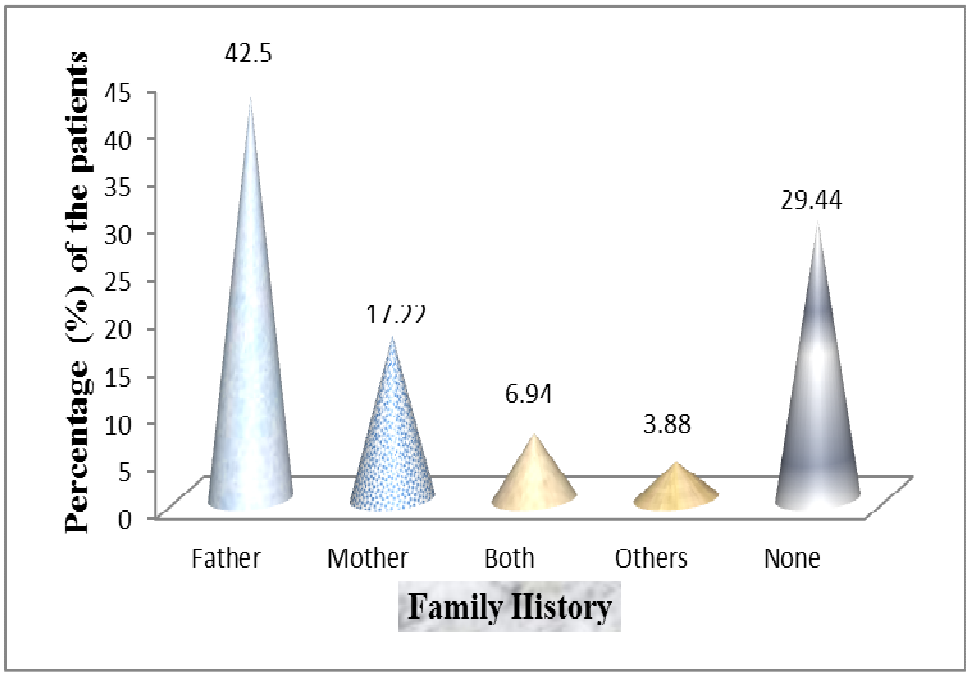


Table – 13: History of raised blood pressure of hypertensive patients

History of raised blood pressure	*Number of patients (n=360)*	*Percentage (%) of patients*
Within Past 12 months	8	2.22
1 to 5 years	132	36.66
5 to 10 years	192	53.33
More than 10 years	28	7.77

Figure – 13: History of raised blood pressure

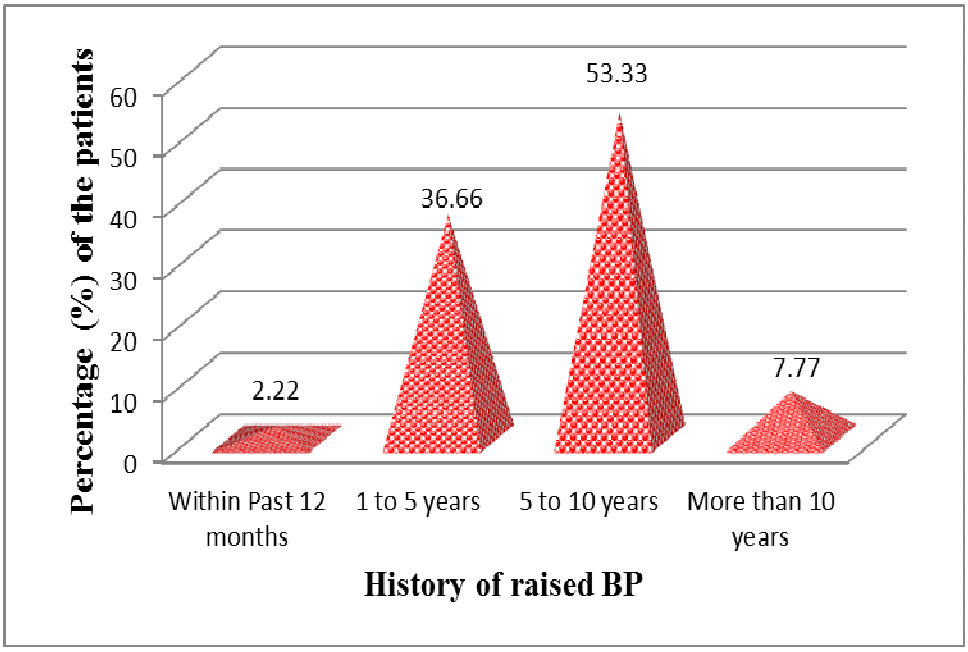


Table - 14: Type of therapy preferred in hypertensive patients

Type of Therapy	*Number of patient (n=360)*	*Percentage (%) of therapy Preferred*
Monotherapy	184	51.11
Two drug therapy	120	33.33
Three drug therapy	40	11.11
Four drug therapy	16	4.44

Figure – 14: Type of the therapy in hypertensive patients

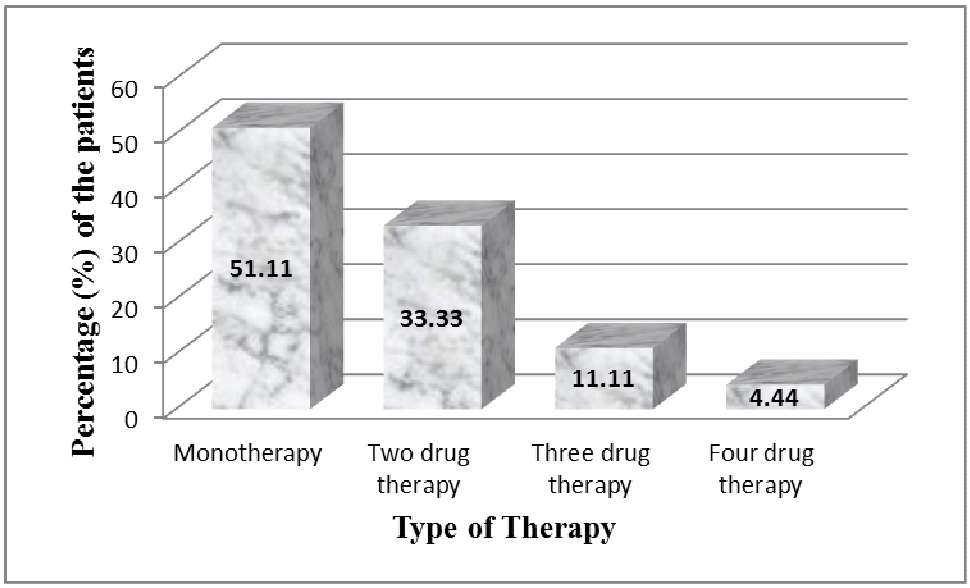


Table – 15: Classes of antihypertensive drugs used to treat hypertensive patients

MONOTHERAPY

Classes of drugs	*Number of patients (n=184)*	*Percentage (%) of drugs prescribed*
β-Blockers	80	43.47
Calcium Channel Blockers (CCB)	66	35.86
Angiotensin II Receptor Blockers (ARB)	28	15.21
Angiotensin Converting Enzyme Inhibitors (ACEI)	6	3.26
Diuretics	4	2.17

CCB: Calcium Channel Blockers **ARB:** Angiotensin II Receptor Blockers

ACEI: Angiotensin converting enzyme inhibitors

Figure – 17: Classes of drugs in hypertensive patients for mono therapy

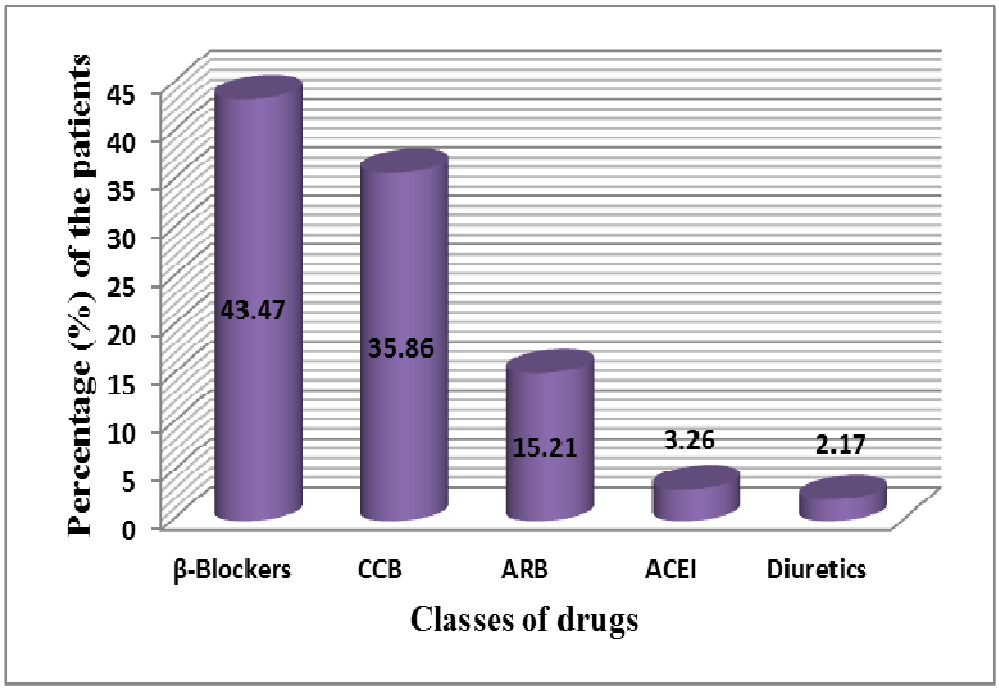


Table – 16: Classes of antihypertensive drugs used to treat hypertensive patients

TWO DRUG THERAPY

Classes of drugs	*Number of patients (n=120)*	*Percentage (%) of drugs prescribed*
CCB + β-Blockers	46	38.33
ARB + CCB	26	21.66
ARB + Diuretics	22	18.33
CCB + ACEI	9	7.5
CCB + Diuretics	9	7.5
β-Blockers + Diuretics	4	3.33
β-Blockers + ACEI	4	3.33

CCB: Calcium Channel Blockers **ARB:** Angiotensin II Receptor Blockers

ACEI: Angiotensin converting enzyme inhibitors

Figure – 16: Classes of drugs in Combination therapy

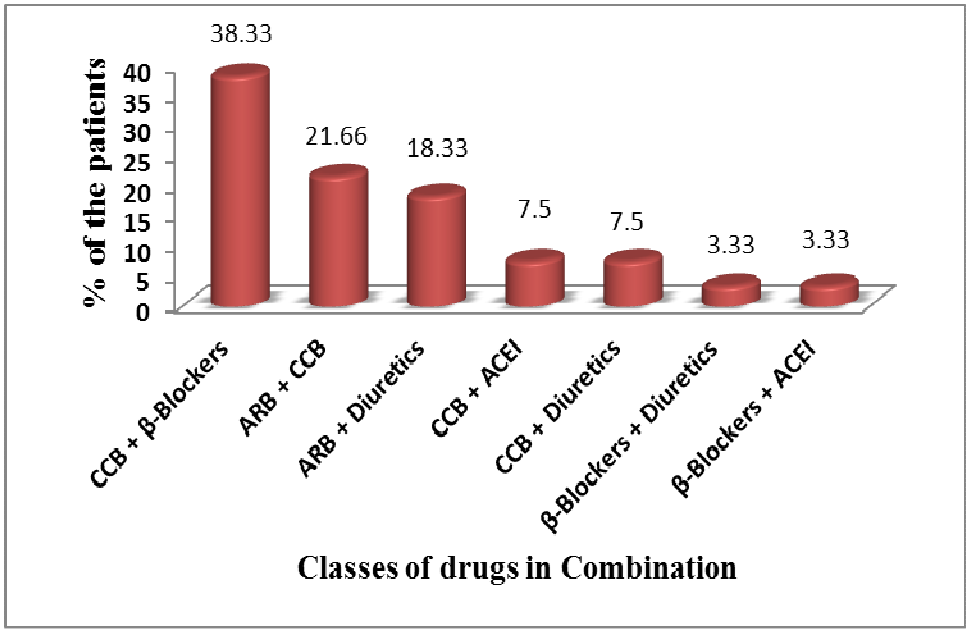


Table – 17: Classes of antihypertensive drugs Used to treat hypertensive patients

THREE DRUG THERAPY

Classes of drugs	*Number of patients (n=40)*	*Percentage (%) of drugs prescribed*
ARB + Diuretics + β-Blockers	12	30
ARB + CCB + β-Blockers	10	25
β-Blockers + CCB + Diuretics	6	15
CCB + ACEI + β-Blockers	6	15
ARB + Diuretics + CCB	6	15

CCB: Calcium Channel Blockers, **ARB:** Angiotensin II Receptor Blockers

ACEI: Angiotensin converting enzyme inhibitors

Figure – 17: Classes of drugs in three drug therapy

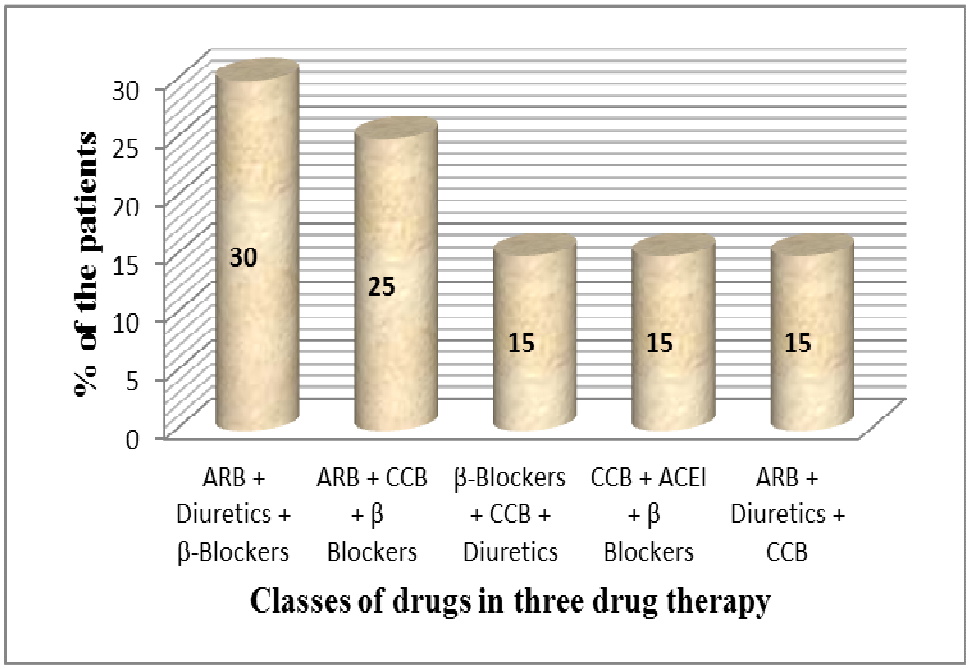


Table – 18: Classes of antihypertensive drugs used to treat hypertensive patients

FOUR DRUG THERAPY

Classes of drugs	*Number of patients (n=16)*	*Percentage (%) of drugs prescribed*
ARB + Diuretics + β-Blockers + CCB	9	56.25
CCB + ACEI + β-Blockers + Diuretics	7	43.75

CCB: Calcium Channel Blockers **ARB:** Angiotensin II Receptor Blockers

ACEI: Angiotensin converting enzyme inhibitors

Figure – 18: Classes of drugs in four drug therapy

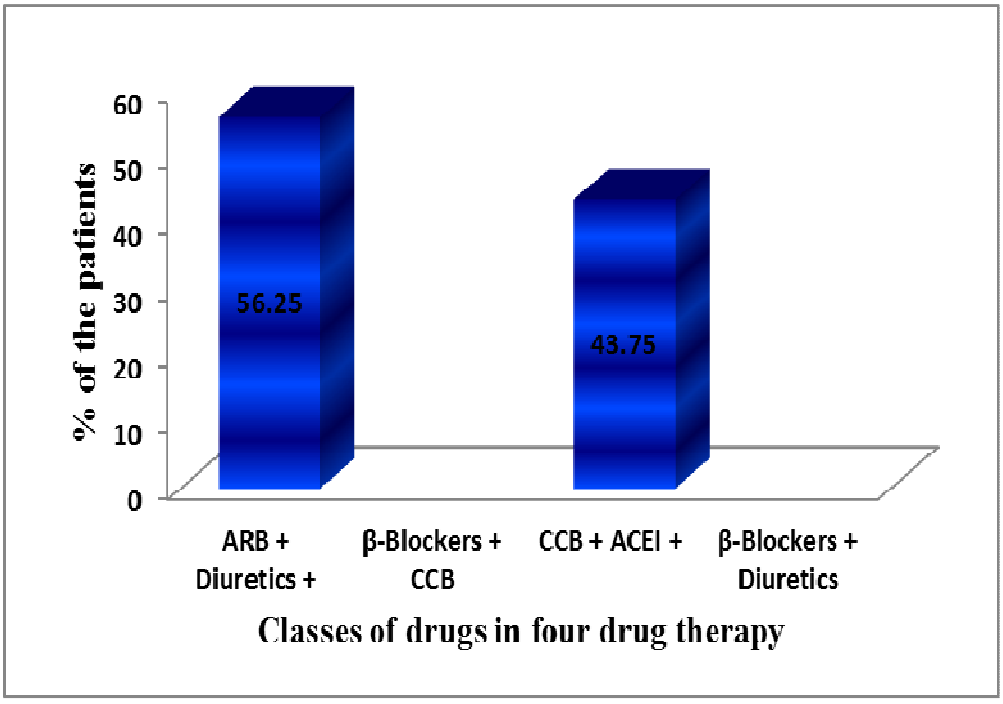


Table – 19: Prescribing pattern of antihypertensive drugs for hypertensive patients

MONOTHERAPY

Drugs prescribed	*Number of patients (n=184)*	*Percentage (%) of drugs prescribed*
Metoprolol	71	38.58
Amlodipine	66	35.86
Telmisartan	12	6.52
Atenolol	10	5.43
Olmesartan	8	4.34
Losartan	8	4.34
Enalapril	3	1.63
Ramipril	2	1.08
Propranolol	2	1.08
Perindopril	1	0.54
Furosemide	1	0.54

Figure – 19: Prescribing pattern of monotherapy

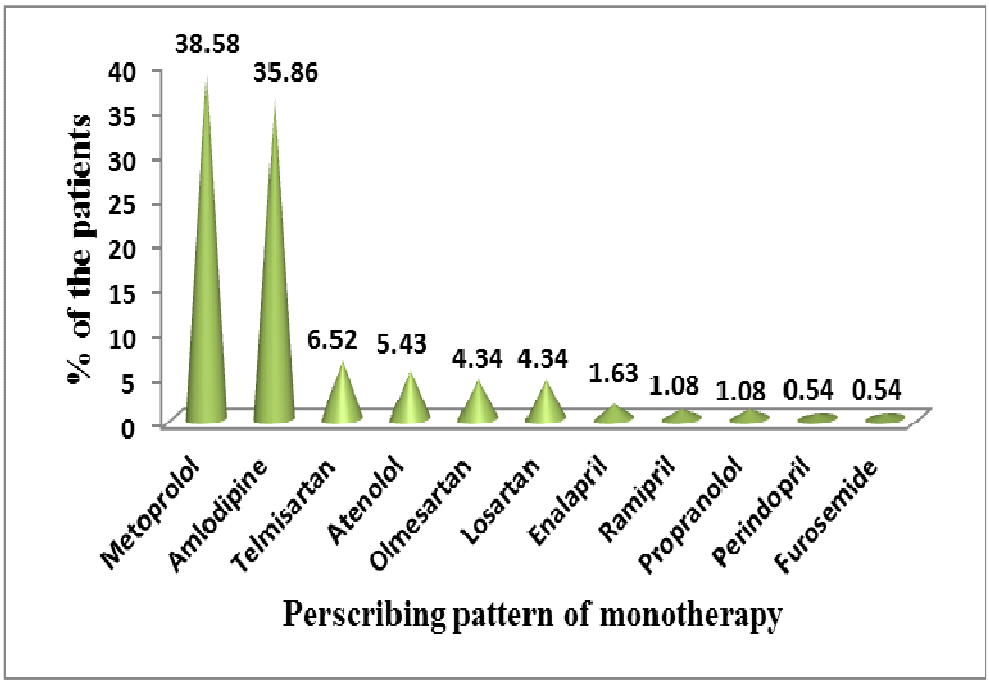


Table – 20: Prescribing pattern of antihypertensive drugs for hypertensive patients

TWO DRUG THERAPY

Drugs prescribed	*Number of patient (n=120)*	*Percentage (%) of drugs prescribed*
Amlodipine+Atenolol	44	36.66
Telmisartan+Amlodipine	39	32.5
Telmisartan+Hydrochlorothiazide	11	9.16
Amlodipine+ Hydrochlorothiazide	8	6.66
Amlodipine+Lisinopril	6	5
Losartan+Hydrochlorothiazide	3	2.5
Olmesartan+Hydrochlorothiazide	3	2.5
Enalapril+Amlodipine	2	1.53
Amlodipine+Metoprolol	1	0.83
Metoprolol+Enalapril	1	0.83
Atenolol+Torsemide	1	0.83
Amlodipine+Torsemide	1	0.83

Figure – 20: Prescribing pattern of Combination therapy

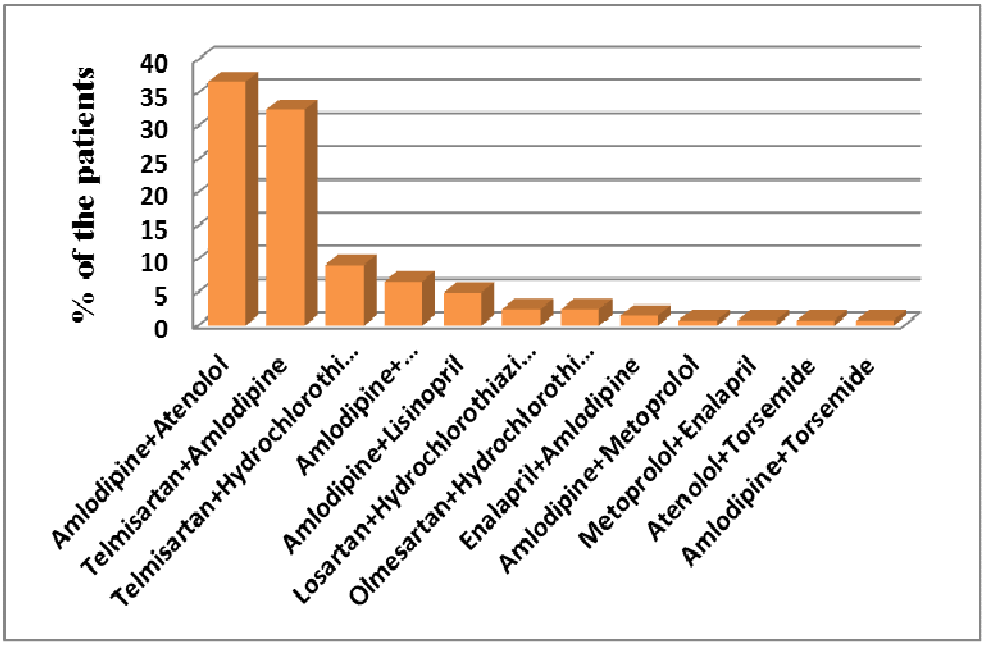


Table – 21: Prescribing pattern of antihypertensive drugs for hypertensive patients

THREE DRUG THERAPY

Drugs prescribed	*Number of patient (n=40)*	*Percentage (%) of drugs prescribed*
Telmisartan+Hydrochlorothiazide+ Metoprolol	15	37.5
Furosemide + Amlodipine + Atenolol	8	20
Metoprolol + Amlodipine + Enalapril	7	17.5
Losartan + Amlodipine + Hydrochlorothiazide	7	17.5
Telmisartan + Amlodipine + Metoprolol	3	7.5

Figure – 21: Prescribing pattern for three drug therapy

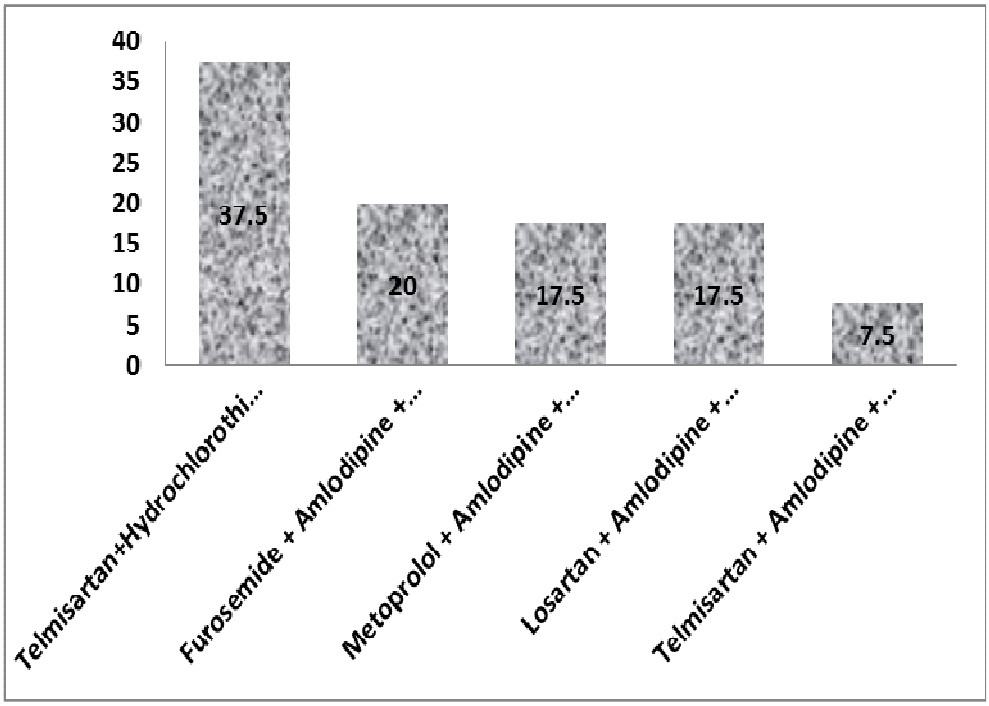
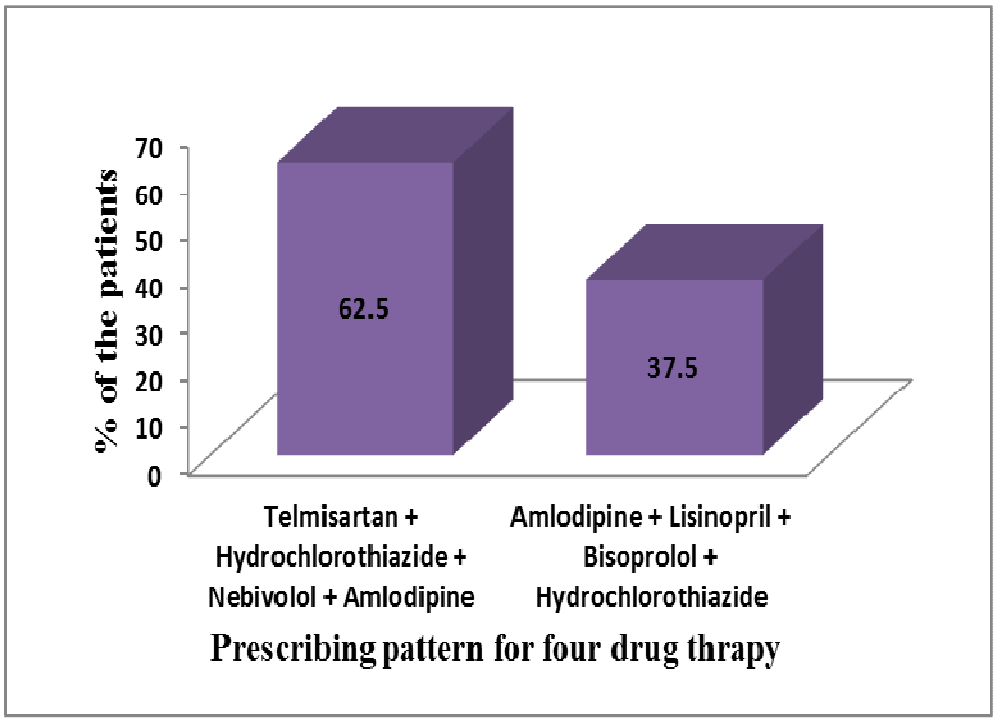


Table – 22: Prescribing pattern of antihypertensive drugs for hypertensive patients

FOUR DRUG THERAPY

Drugs prescribed	*Number of patient (n=16)*	*Percentage (%) of drugs prescribed*
Telmisartan + Hydrochlorothiazide + Nebivolol + Amlodipine	10	62.5
Amlodipine + Lisinopril + Bisoprolol + Hydrochlorothiazide	6	37.5

Figure – 22: Prescribing pattern for four drug therapy



RESULTS AND DISCUSSION

The present work was carried out to determine the treatment differences between patients having hypertension.

Distribution of hypertension:

Gender wise distribution

A total of 360 patients having hypertension were analyzed, in that 196 patients (54.44%) were male and 164 patients (45.55%) were female (Table-1).This result was similar to the study conducted by Chobanian AV et al[4] also reported that male patients were more prone to hypertension.

Age wise distribution:

In this study, different age groups were observed and higher prevalence of occurrence of hypertension was found in the age group of 55-64 years. In that 144 patients (40%) were hypertension, followed by age group of 45-54 were 82 patients (22.77%) hypertension, age group of 65 and above were 62 patients (17.22%) hypertension (table-2).

There was no significant difference in the age or sex when compared to the groups of hypertension. Similar result was observed by White et al [31].

Distribution based on Body mass index (BMI):

From the study, it was observed that hypertensive patients (194 patients) were more due to overweight category (53.88%) according to body mass index(BMI) (Table-3). Similar results were observed by Choo V et al [11].

Distribution based on residential area:

Table- 4 revealed that patients living in urban areas (186 patients) were found to show higher prevalence of hypertensive (51.66%) compared to those living in rural areas. This result was similar to the study conducted by Chadha SL et al [10].

Distribution based on occupation:

From the study, it was observed that hypertensive patients (192 patients) were more since they are manual workers (53.33%) (Table-5). Similar results were observed by Dubey VD et al [12].

Distribution based on sanitation:

From the study, it is observed that hypertensive patients (264 patients) were more due to their habitat in noisy zone (73.33%) (Table-6). Similar result were noticed by White et al[31] .

Distribution based on work stress/ sleep disturbance:

From the study, it was observed that hypertensive patients (265 patients) were more due to work stress (73.61%) (Table-7).

Distribution based on food consumption:

From the study, it is observed that hypertensive patients (304 patients) were more consumption of non-vegetarian varieties of food (84.44%) (Table-8). This result was similar to the study conducted by Appel LJ et al[24].

Distribution based on tea/coffee consumption:

Caffeine antagonises endogenous adenosine which causes vasoconstriction, this increases peripheral vascular resistance leading to increased blood pressure. Milk and milk products reduce the level of saturated fatty acid by complimentary mechanism thus lowering the blood pressure. This was also reported by Srinath Reddy K et al[41].

Table-10 revealed that patients consuming coffee / tea (258 patients) were found to show higher prevalence of occurrence of hypertension (71.66%) than the general population (Table-10). Similar results were observed by Srinath Reddy K et al[41].

Distribution based on behavioral risk factors:

From the study, it was observed that hypertensive patients (146 patients) were more due to smoking, alcohol and tobacco chewing (40.55%) (Table-11).

Intake of OTC drugs (NSAID drugs) becomes a behavioral risk factor and it leads to cause hypertension in 5.55% of patients (Table-11). Similar results were observed by Akici et al[29].

Drug prescribing pattern:

Type of therapy:

In hypertension patients, monotherapy (51.11%) is mostly preferred (Table-14), followed by combination therapy (33.33%).

Monotherapy:

In hypertension patients, β-blockers (43.47%) are mostly used classes in monotherapy (Table-15). Where in Metoprolol (38.58%) is mostly prescribed (Table-19). This result was similar to the study conducted by Tiwari et al[28].

Combination therapy:

Two drug therapy:

In hypertension patients, β-blockers with calcium channel blockers (CCB) (38.33%) are mostly used classes in two drug therapy (Table-16). Where in amlodipine with atenolol (36.66%) were mostly prescribed (Table-20).

Three drug therapy:

In hypertension patients, angiotensin receptor blockers ARB**,** diuretics and β-blockers (30%) were mostly used classes in three drug therapy (Table-17). Whereas telmisartan**,** hydrochlorothiazide and metoprolol (37.50%) were mostly prescribed (Table-21). This result was similar to the study conducted by Tiwari et al[28].

Four drug therapy:

In hypertension patients, angiotensin receptor blockers ARB, diuretics, β-blockers and calcium channel blockers (CCB) (62.5%) and calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), β-blockers and diuretics (37.5%) were used classes in four drug therapy (Table-18). Whereas Telmisartan**,** Hydrochlorothiazide, Nebivolol and Amlodipine (62.5%) and Amlodipine, Lisinopril**,** Bisoprolol and Hydrochlorothiazide (37.5%) were prescribed (Table-22).

CONCLUSION

The study concluded that there was no significant difference in prevalence of occurrence of hypertension between male and female.

The prevalence of hypertension was found to be more in older than in younger patients.

In the present study, overweight category peoples were more prone to hypertension, diabetes and other cardiovascular diseases.

From the socioeconomic status, those living in urban areas and noisy zone were found to show marked attribute to hypertension.

From the present study, those people who consume more of non-vegetarian kinds of food, excess oil and coffee/tea were more prone to hypertension.

In the current study, alcoholics and smokers were found to show marked attribute to hypertension and also those who intake OTC drugs (NSAID's) increases the risk.

Life style modification (proper diet, regular exercise) in patients can also help in controlling blood pressure.

Anti-hypertensive drugs must be selected in such fashion that it should be safe and should not worsen concomitant co-morbidies diseases.

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ANNEXURES

ANNEXURE - 1

DATA ENTRY FORM

Name of the Patient: **Date:**

Gender: Male / Female **Place of Survey:**

Age Group: ☐ 18 – 24 ☐ 25 – 34 ☐ 35 – 44 ☐ 45 – 54 ☐ 55 – 64 ☐ 65+

Weight: **Height:** **BMI:** ☐ Normal Weight ☐ Underweight ☐ Overweight ☐ Obesity

Residence: ☐ Urban ☐ Rural ☐ Mixed

Education: ☐ Illiterate ☐ Primary (1 – 5) ☐ Secondary (6 – 10) ☐ Higher Secondary (12th) ☐ Degree

Marital Status: ☐ Married ☐ Never Married

Occupation: ☐ Executive / Business ☐ Agriculture ☐ Domestic ☐ Services / Sales (Marketing)

☐ Manual Workers

Sanitation: ☐ Noise free zone ☐ Noise Pollution

Stress : ☐ Normal sleep ☐ Sleep Disturbance / work stress

Food Consumption: ☐ Vegetarian ☐ Non-vegetarian

Oil Consumption: ☐ Coconut Oil ☐ Groundnut Oil

☐ Sunflower Oil ☐ Soybean Oil

☐ Palm Oil ☐ Mustard Oil

Dairy Consumption: ☐ Milk

☐ Coffee / tea

☐ Health Drinks

☐ None

Behavioral Risk Factors: ☐ Smoking (Beedi / Cigarette)

☐ Tobacco ☐ OTC drugs (NSAID's)

☐ Alcohol

Family History of Hypertension: ☐ Father ☐ Mother

☐ Both ☐ Others ☐ None

History of Previous Hospitalization: ☐ Government Hospital

☐ Private Hospital

Diagnosis: ☐ Hypertension

Blood Pressure Reading: Systolic _____ (mm/Hg)

Diastolic _____ (mm/Hg)

History of Raised Blood Pressure:

- ☐ Within Past 12 Months
- ☐ 1 to 5 Years
- ☐ 5 to 10 Years
- ☐ More than 10 Years

Medication Prescribed

S.No	Brand Name	Generic Name	Dose	Route of Administration	Frequency

Health Professionals Advice:

- ☐ Quit Smoking
- ☐ Quit Alcohol
- ☐ Dietary Modification
- ☐ Reduce Salt Intake
- ☐ Lose Weight
- ☐ Increase Physical Activity

ANNEXURE – 2

INFORMATION FOR STUDY SUBJECTS

Dear participant,

I **FATHIMA BEVI A** student of J.K.K.NATTRAJA COLLEGE OF PHARMACY currently conducting a project entitled "A prospective study of prescribing pattern of antihypertensive drugs in a tertiary care hospital" for the partial fulfillment for the award of degree of Master of Pharmacy in Pharmacy Practice.

As the part of project i need to collect demographic data, identify the prescribing pattern of antihypertensive drugs.

I will appreciate very much if you could kindly assist me to collect your medical data's. However identifiable personal data's will not be disclosed.

Thank you very much for your kind participation.

CONSENT FORM

I, _____, have read and understand the above information. I have agreed to allow my data to be collected for the project work.

_____

_____

Signature of participant Date

_____

Signature of translator

ANNEXURE – 3

- **Want to paste ethics certificate here**
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